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THE JOURNAL OF PEDIATRICS

A MONTHLY JOURNAL DEVOTED TO THE PROBLEMS AND DISEASES OF INFANCY AND CHILDHOOD

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Original Communications

A PEDIATRICIAN LOOKS AT PSYCHIATRY

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WHEN one has been in practice for fifty-four years, he has seen many changes, not only in techniques and methods but in beliefs, points of view, and in guiding philosophies.

What were truisms when he began, are now held to be without the slightest foundation in fact. Cherished treatments, unquestioned etiologies, even diagnostic entities, have disappeared into the limbo of forgotten ideas.

In his daily work, the doctor of the late nineteenth century found his major tasks, and his living, in the care of "dirt diseases"—typhoid, dysentery, diphtheria, tuberculosis of bones, joints, glands, and lungs, chronic septicemic states, with osteomyelitis of the long bones and of the mastoid as daily complications. It was not more than twenty-five years before 1896 that a great French surgeon had stigmatized the operating room as the "antechamber to death."

By 1896, the Pasteur-Koch teaching about the etiological role of bacteria and related living organisms was accepted, but not fully. There were many skeptics among the medical men.

But the lessons soon came to be clear enough, especially as they came to be re-enforced by the brilliant applications of public health experts. With these developments, even practicing doctors began to see the decisive part that objects and events in the physical environment play in the production of diseases of the human body.

At that time, too, the theories of Charles Darwin were beginning to attain wide acceptance. "Organic evolution" by adjustment of living beings to conditions of the environing world—survival for those individuals able to adapt themselves to the favorable and unfavorable activities of forces inherent in the environment, and death or disease for those unable or unwilling to make the needed adjustments were accepted as facts.

Later the physicists and chemists, and mechanics, too, were riding high in the fields of biology, especially in medicine. So much so, that in 1900 it was believed that the metabolism of the human organism could be estimated and reported in terms applicable to any machine, in terms of calories of fuel intake, balanced against the heat equivalent of work, plus a material supply sufficient to keep the body in repair, that is, of nitrogen and minerals, enough to replace the wear and

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tear of the machine. This was held completely to explain life and living. The philosophy guiding the medicine of the time was essentially and completely materialistic—the kind of thing that led to rugged individualism, the kind that hailed man as an autonomous, free agent, able on his own terms to throw monkey wrenches at will into the cosmic machinery!

All this became obsolete when Gowland Hopkins proved man's need for "accessory foodstuff" (they later came to be the badly named "vitamins"); enzymes, without which calories, proteins, fats and carbohydrates, taken from the environment, are without power to keep the body functioning effectively. An added blow was given to the sufficiency of this mechanistic concept as more attention came to be paid to Claude Bernard's profound concept of the internal environment; of the *milieu interne* maintaining itself automatically within very narrow limits, physical and chemical, balancing itself against the violent variations of the *milieu externe*, the external environment in which the organism has to survive.

Thus, again, emphasis was laid on the importance of the relation between organism and physical environment. Another influence that appeared to modify the clinician's approach to the study and management of sickness, and the sick, stemmed from Hughlings Jackson's concept of a human nervous system evolving level by level from its earliest appearance in the simpler multicellular creatures, and arriving eventually at the present complexity of the human central nervous system. By the beginning of the twentieth century this study of comparative evolutionary neurology had convinced clinicians that mental activity is "not the function of any one portion of the brain, but depends upon the associated activity of many parts—some more important to the process than others."*

Although Freud was laying the foundations for his brilliant, helpful concepts in those days, he had not yet given those decisive Lectures (1909) to Americans at Clark University in Massachusetts—lectures that started psychological analysis on its vigorous and persisting way in the United States. Without any doubt, Freud, disciple of Charcot and Janet, was influenced in his concept of the unconscious by pondering Jackson's doctrine of successive levels of neural apparatus evolving to meet the survival needs of each organism as it appeared and ascended the developmental scale of ever-increasing complexity. The theory posed that the apparatus of each lower level remained functioning in the higher, so that man with his complicated central nervous system is bound to many of the simple, violent functional expressions of his primitive ancestors. For instance, those aspects of mental activity endowed with emotional or affective tone are closely related to vegetative life, which is mainly integrated in the hypothalamus. Sleep can be thought of as a temporary suppression of consciousness. By experiment and by clinical observation sleep has been shown to be regulated in the hypothalamus. Out of this concept, Freud reared his famous doctrine of the Unconscious Mind and the crippling conflicts of the Super Ego, the Ego, and the Id, which, after all, is a poetic psychologist's way of treating the medieval concept of God, the World, the Flesh, and the Devil. In

*Gordon Holmes.

the sixteenth century, Pico della Mirandola, the greatest of Italian humanists, put it this way: "Man is a little world; a body mixed of earthly elements and ethereal breath; the vegetative life of plants; the senses of lower animals; the reason and intelligence of angels, and a likeness to God." This is very like a foreshadowing of Freud's nineteenth century Super Ego, Ego, and Id: Mirandola's "intelligence of the angels and likeness to God," the Super Ego, his "man" the Ego of Freud, and his "senses of lower animals" Freud's Id.

The trained pediatrician whose premedical experience was predominantly physiological and humanistic was naturally sympathetic with this point of view. As Addis has pointed out, the clinician is interested chiefly in what he conceives to be a "cause" for the disease or disorder he has to deal with, and then only if the "cause" is a removable one whose eradication will ameliorate or remove the disease or, at least, its symptoms. The clinical training of clinicians in the earlier days of medicine was biological and based on physiology and pathology, which, at the dawn of the twentieth century, was beginning to be increasingly influenced by chemistry and physics, which, as biochemistry, were supplementing bacteriology, and to some degree lessening its dominance in the clinical field.

The sum of such clinical and preclinical training usually left the doctor a convinced materialist—an individualist, whose concept of himself and his fellows pictured them as autonomous masters of themselves, responsible for the use of their free will, and guilty and punishable if they failed to make profitable use of their opportunities. Children were considered little other than imperfect adults, responsible within the limits of their stage of maturity for their behavior, and it was the parent's duty to train them to become useful citizens according to the best pattern available, and that pattern usually was the parent—as he thought he was, or as he would like to have been.

Such was the background of most clinical pediatrists forty or fifty years ago. Pediatric texts of the time made little reference to any illnesses other than somatic disturbances. Pathological deviations from normal physiological function were sought (and usually found) to explain a host of disorders that now are treated as neurotic or neuropsychotic deviations.

We were busy dealing with vomiting babies, wasting babies, marasmic babies, desiccated babies' anorexias, second summer diarrheas; hard at it treating peritonitis following ruptured appendices, or mastoiditis from neglected otitis; osteomyelitis; pyemias and pyurias. The surgical-minded, rarely idle, occupied themselves with removing tuberculous neck glands or dealing with tuberculosis of the spine, the long bones, or the peritoneum. Health officers' tasks grew in number and importance. In a little while they had robbed practitioners of those sources of income, and made it very clear to us how greatly the health of the individual depended on ability to control the physical and social environment of the child. The loss of those sources of income focused the attention of the pediatrist on preventive pediatrics, and preventive pediatrics in turn called attention to the fact that the home was the environment of the child, and that bad technique in the home was responsible for many, if not most, chil-

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dren's diseases, whether of body or mind. Also, with the coming of preventive pediatries, the doctor was forced more often to confer with the parents, to plan with them to help improve techniques of home management and of child care. With this trend came his own discovery of the total situation concept. It became clear that neither child nor parent is an autonomous individual independent of the life situation in which it has to exist. And, for the child, that controlling situation includes the parents, other adults, the physical environment, the social pattern that guides parents in their behavior, and through them, supplies the background in which the child must manage to survive. And not least, in this total situation, is what the child thinks and how he feels about all this. In other words, at long last, the pediatrician came to the conclusion that the *personality* of the child is a resultant of the forces of its inherited endowment, pre-human and human, the forces arising from objects and events resident in the surrounding world, and the thoughts and actions and stored memories these objects and events arouse as stimuli acting on the organism.

Man has come to understand the inwardness of the gravitational process, and recognizing that inwardness, following the discoveries of Copernicus, Galileo, and Newton, he brought modern science into being; and, through it, Mankind was able to harness the force of gravity and so to bring about the industrial age, the aviation age, and the revolutionary (to some revolting) age of atomic energy. Discovering, accepting, extending, and utilizing the laws of chemistry, of physics, and of mechanics, all of them sprung from this fundamental concept, Man has built up the body of knowledge and of guidance which we know as the physical sciences on which modern industry is founded.

Man has used no such energy or wisdom in dealing with that part of nature that treats of his own personal relations to the environing world. Included in this part of nature are the individual man's interactions with his surroundings, his social responses to other people, his psychical reactions to the thoughts and feelings aroused within him by the impact of all these influences. And yet, in this field, for guidance there has been enunciated a great fundamental principle—a principle in its way as important for human behavior, psychological and social, as gravitation is for mechanics.

Shortly, that principle is that Man does not and cannot exist except as a part of the total life situation in which, at any given moment, he finds himself. This principle is as exigent and as unchanging as that which states that physical bodies remain in their previous state of motion or rest until acted on by some external force. As a result of this principle there is no such thing as a free organism behaving according to an occultly directed will. Detached from the physical and social objects and events impinging on that organism from that environment, there can be no personality.

The personality which behaves is a complex of organism, physical environment, and social contacts—a fabric of symbols and memories, some false, some fantastic. There enters into this complex, not only these influences, but others as well—modifying, restraining influences that come from the past, some through the ancestral genes, some

through the inheritances of mass cultural experiences of the social group of which the individual is a part. Once these views are generally accepted, it may be possible to produce a new generation of understanding citizens, citizens who will be able to comprehend the means at hand which will discourage destructive antisocial activities and will encourage those social views and actions that are constructive and righteous.

Another important factor in estimating the life situation of the children is the fact, too often ignored, that no part of the situation for children is static. The child is constantly changing as it grows toward maturity, and its world increases in extent and complexity from day to day, almost from hour to hour; and what it thinks or feels changes, too, so that each child has to be dealt with as an individual whose personality is in constant flux. This is one of our grave handicaps in dealing with immaturity. Another difficulty, even more important, comes from the usual lack of appreciating the child's vague notions of what words mean to the grownup who uses them. Verbal concepts come slowly, imperfectly, and develop in a confused way in the minds of children.

To go back to our clinician. In the meantime, much of his experience was accumulating to re-enforce his conviction that the mind was the expressive function of a healthy central nervous system. He remembered Vesalius' statement: "I know nothing of the seat of the soul, but I do know that without the brain there is no possible expression of the soul—no consciousness."

And there was plenty of clinical evidence that the damage to subcortical structures in encephalitis lethargica, which was absent or little noticed in practice before the early 1920's, could be followed by profound changes in behavior. Tuberculous meningitis, brain abscess and brain tumors, and various epidemic appearances of Weichselbaum's meningococcus meningitis testified that such psychical disturbances as deterioration of mental capacity, emotional instability, dulling of consciousness, stupor, coma, convulsive seizures, changed personality, hallucinations, and disorientation—any or all—may happen in central nervous system disease that is limited to, or maximum in, the upper midbrain and the hypothalamic region.

Considering his training and experience in practice, the pediatrician of the early decades of the twentieth century, as all other clinicians and physiologists of the time, concluded that consciousness and mental processes depended on the physiological activity of the upper levels of the nervous system acting as a whole. Later on it came to be accepted that certain more specific aspects of mind rested on the healthy functions of special areas of the brain; and, largely thanks to Cannon's fundamental work, it seemed to be proved that emotional expression was a function of the autonomic nervous system and its closely linked endocrine complex.

Thus it came about that most of the discoveries in biology, especially in its neurological aspects that followed one after the other at a tremendous pace, tended to confirm the clinician in his conviction that behaviors could be defined in terms of the nervous system's functional ability to achieve adjustment between the organism and environment.

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It was just then that Freud's doctrines began to be authoritative enough to influence clinical medicine. Freud, himself, was a master clinician, a neurologist of established reputation, but also a scholar deeply versed in philosophy and the history of philosophy and able to understand and apply the teachings of the then rather new discipline of anthropology, a discipline which his theories and doctrines later were to revolutionize. Since then, fiction, biography, and history, in fact every intellectual endeavor, has felt the impact of Freud's theories.

More and more as pediatricians and public health workers reduced the incidence of dirt disease and malnutrition, the behavior problems of children loomed larger and larger. It became more and more apparent that the changes in the style of life, changes from rural to urban living, also contributed greatly to the appearance of these problems. A notable and profitable discussion of this aspect of the problem is to be found in J. L. Halliday's *Psychosocial Medicine*.*

Freud brought ample evidence to show that adult neurotics suffered from the effects of emotional damage and unhappiness visited on them in childhood as a result of misunderstanding, ignorance, carelessness, or sometimes of the brutality of adults, too often, of parents. That fundamental tenet of Freudianism fitted aptly into the pediatrician's need for "a cause" and it confirmed and gave a pattern to his own observations and to the rather vague patterns he had been evolving in his attempts to devise a therapy for the behavior anomalies and neuroses of children.

Above all, it offered an opportunity to devise schemes of advice that might be preventive of disastrous deformities of adult personality such as the Freudians were discovering and treating. It is unfortunate that such schemes came to be called child guidance, rather than family reorganization, for Freud's pioneering certainly strengthened the hands of pediatrists who realized that the total situation from which the maturing child's personality derived was, at least to school age, almost entirely the family situation and, after that, until work or college days arrived, very largely so. This point of view is amply justified daily in the experience of this clinic.

Fundamental as was Freud's point of view for clinical pediatrics, his methods of exposition and many of his supporting theories were so opposed to the neurological concepts of psychic function then held by clinicians that they were rejected with vigor, sometimes with venom. It seemed to many of those whose experience with children was extensive and profound that the infantile sexuality theories were built up on a foundation of assumption. It seemed that thoughts and feelings ascribed to infants and summoned to support the theories were essentially adult in quality; that they could have been acquired only by virtue (or vice) of adult or adolescent experience. Thus, few experienced pediatricians were able to persuade themselves that the children they had known so thoroughly had ever thought or felt in these ways. It may have been that the verbal patter of psychiatry put the simple-minded clinician off: narcissistic, dysmnesic, masochistic, sadistic, hebephrenic, and a host more got the profession into the frame of mind of the Yorkshire laborer, who, strolling along with his pal, saw an unknown

*W. W. Norton & Company, 1948.

figure walking toward him, and said, "Yon's a stranger, Bill, heave a half a brick at him."

When the great schism arose in the analytic order, when disciples Jung and Adler differed with the master, clinicians learned a lot from the pros and cons that were batted back and forth. As the pediatrists saw it, the fundamentals were unshaken but the ornamental explanations suffered some damage. Those of us who had to deal with families that hoped to bring up children to be useful, happy citizens found little of use for our purposes in the mystical deviations of Jung. Much as they may have respected him and admired his integrity and ingenuity, what he offered for preventive pediatrics could be found in large measure in the current religions. I mean that he offered little applicable to help erect a plan of family relations that would secure the happy, contented, satisfyingly occupied childhood essential to the development of a personality free from neurotic disabilities. For adults, doubtless, he has much to offer and brings comfort to many.

But of the other major heretic, Adler, the story differs. His deviation served to maintain the analytic fundamentals useful to the clinical pediatrist. His assertion that unsatisfied self-assertion (repressed ego) is the main cause of neuroses appeals to the pediatrist who often sees in his families the process of undue ego repression going on at the hands of siblings, parents, nurses, and other adults. At the school age, some teachers seem to think such suppression is their major function. The damage to this ego factor in the total situation comes, not alone from the repression, but from the emotional reactions to it, and above all, to the affect that the child stores, to become his sense of justice or injustice, his spirit of revolt or of submission.

Adler makes less use of symbolism than Freud or Jung. To the clinical minded, it seems that the symbolists often create their symbols without logic and then apply them imaginatively to explain difficult situations. Adler rejects the view that the simple bodily reactions of an infant determine his subsequent adult trends. For instance, it seems probable to him that a miser is such not because as an infant he was "an anal neurotic." One, he holds, must recognize that such an infant is at a stage of immaturity at which his capacity for reaction is very limited and the world of objects and events which can stimulate him is exceedingly restricted. For Adler, what he calls the "style of life" is established in the first five or six years of childhood. Thereafter, the acquired pattern persists as an automatic guide to the reactions evoked in response to the various situations in which the child finds himself. This is a concept that the pediatrician's own clinical experience supports abundantly.

The child's desire to assert himself springs from the need for the young to learn to manage their own inherent powers. Instinctively, he is seeking for security as a person in a hostile environment. That power motive will express itself in various children according to the life situation of which each is a part in struggles with parents, siblings, nurses, or other adults. It will be quite different in an only child, a first-born, a second, or a youngest child. From this comes one of the pediatrician's g r e a t e s t difficulties.

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Parents rarely realize that in the same home, no two of their children secure an identical environment any more than any two are endowed with the same germ plasm by inheritance.

Long before the days of Freud or Adler, the pediatrician had it impressed on him that the family is the place in which the child is taught or trained or conditioned to meet the exigent demands of his limited world, and that in meeting these demands, he establishes behavior reaction patterns that will be his until he dies. These are patterns, whose use in adult life will determine the degree of success or failure he will have in meeting the shifting situations that he will encounter in the wider, more complicated world of the grownups. The pediatrician saw that, in the family circle, the child learns how to master his own bodily movements and by the aid of these movements acquires the skill needed to use the gadgets and behavior patterns current culture imposes. But, even more important still, by his own observation and by imitation of his elders and his siblings, the little one learns to react to strangers and to friends, learns what it means to have his actions measured by comparison with those of another child, or by a parental standard arrived at through the father's or mother's past experience, experience gained under social and cultural conditions very far from those their home provides for their children in this day and generation. Very often, the demand that he meet such standards is a source of confusion and uncertainty for the child, a cause for unhappiness that leads him into revolt against, or on the other hand, into overdependence on the pattern of authority. In the family, too, the pediatrician sees the child learning what competition means. Later, in school, he sees the youngster subject to additional doses of competition with its resulting successes or failures, and if he is lucky, teaching himself how to deal with these inevitable stresses and strains. Here, under the doctor's eye, attitudes are established in response to what the child estimates as failure or success, what he feels as pleasure or pain, of reward or punishment. Such attitudes come as responses to the expectation of love or dislike, of helpful friendliness or of unkindly criticism. On such attitudes is built what Adler called "Style of Life." This is a concept particularly appealing to the pediatrician because of his day-by-day experience of intimate family life as lived in the homes of many kinds of people.

For the benefit of the child, and of the future society that present-day children will compose, it becomes the pediatrician's paramount task to classify and to emphasize the obvious errors and injustices too often visited on children. These injustices are important beyond words because children, within the limits of their stage of maturity, have very keen appreciation of injustice and justice. The most damaging errors are based upon varying parental attitudes, carelessness, selfishness, harshness, and probably worst of all, the pathological solicitudes of parents and parental overpossessiveness, with an attempt to forcibly impose their own personality pattern on the child, to bring him up to be just like papa or mama, or to avoid the errors and weaknesses the parents think are characteristic of themselves.

Another important duty pediatrists have is to assert the unique individu-

ality of the child and his right to freedom so far as it is compatible with the parent's duty to provide any wisdom they may have gained in their own life experience, recognizing always that the most precious thing for the child is the right to his own experience, the right within the limits of his own world to the rewards of his successes and the pains of his failures. In other words, he has the right to the pleasures and punishments implicit in the trial-and-error approach to experience. Among sources of distress for the young in the parent-child relationship, which the wise doctor tries to impress on his clients, is the adult's unwillingness to grasp how naive and imperfect is the child's understanding of langauge, how different the youngster's concept of the meanings of words. Much distress, as well as many accusations of deceit and lying, is avoided once this peculiarity is made clear. To the pediatrician, not the least important duty of the parent is to teach the child to think about his own behavior and to use his own necessarily imperfect reasoning powers to consider it. To expect the young child to comprehend all the conclusions that parents arrive at, by the way of adult reason (or adult prejudice), is a sure way to confuse the child, to render him uncertain, insecure, and unhappy, and force him into the retreat that all bewildered human beings seek—fantasy. To come down to the level of the child's reasoning powers, and, year by year, as his mind develops, to help him to use what he has to the fullest, to help him to use all his endowment to consider his life situation and his relation to that situation in terms well within the limits of his comprehension, is a service parents and pediatricians owe to children.

It is impossible to detach the child's behavior from the family situation, for therein is the young child's total life situation, at least for the first six or seven years in which the pattern is set, by which the reaction of that human being to the objects and events of the environment will be guided.

This experience fixes the pediatrician's decision as to what parts of the body of psychiatric doctrine he can best use in his attempt to prevent or to alleviate adult, adolescent, and child neuroses, by helping guide intrafamily relationships. As a clinician he gets great practical aid from Adler's view that unsatisfied self-assertion is the main cause of psychoneuroses. An adaptation of this view and of the Adlerian concepts that grow out of it gives the pediatrician as a clinician that "removable cause" that Addis postulates as essential of the clinical point of view, and, too, it gives ways and means of its removal by instruction of parents and adjustment of obviously unhealthy relations within the family circle. This does not mean that the pediatrician overlooks the pioneering contributions of Freud, their essential fundamental value, nor the fact that without Freud, both Adler's and Jung's doctrines would have no ultimate foundation. Erik Erikson postulates the three C's as fundamental to sound family relationships for children: courtesy, certainty, and consistency. The pediatrician knows that behavior problems rarely occur in families whose adult members are uniformly courteous to one another as well as to children of the household.

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To those who may think that wisdom in this field began with the twentieth century psychology, words written in the eighteenth century by Frederick William Schleiermacher may be revealing: "Fathers provoke not your children to wrath, lest they be discouraged.

"If the life of a child be embittered, and the result be shyness and secret aversion, that is the most unnatural state of all. From its beginning the whole being of a child is linked by and is dependent on those who are older . . .

"If the hearts of children be embittered towards us, making them timid in our presence—if their natural trustfulness be turned to hollow suspicions, as if we were seeking our own and not their interests—if love be extinguished and the feeling of confidence lost, where shall we again find the key with which we can open their hearts?"

THE TREATMENT OF EPILEPSY BY CORTICAL EXCISION

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INTRODUCTION

In the past fifty years many different types of surgical procedures have been attempted for the relief of epilepsy. Some have been based upon sound physiological principles, others upon fallacious reasoning. Owing to the capriciousness of the disease and tendency for periods of freedom from attacks to follow almost any change in habit, each procedure initially has been propounded enthusiastically and then allowed to fall silently into discard as time demonstrated the futility of the measure.

Because our knowledge of the epilepsies[4] is so confused, it does not seem wise to attempt a rigid classification at this time. For the purpose of this paper, symptomatic epilepsy will have the connotation that a known factor is operating upon the brain, whereas idiopathic will imply that the etiological factors are unknown. The idiopathic group then includes most of the cerebral dysrhythmias, subcortical epilepsies, and genuine or genetic epilepsies.

It cannot be too strongly emphasized that the primary therapy for a patient suffering from convulsive seizures is medical—anticonvulsive medication, psychotherapy, and social and occupational rehabilitation. *Surgical procedures are no substitute for medical management.* Of course, if there is evidence of a progressive lesion of the brain such as tumor, abscess, hematoma, etc., appropriate surgical measures are imperative, but in the chronic epilepsies medical management is of prime importance.

Operative intervention should be considered when medical management has failed to control the seizures. This implies that those drugs which are commonly considered effective in the treatment of the type of epilepsy involved have been given alone and in combination to toxic limits. In general, seizures due to cortical lesions respond to phenobarbital, diphenylhydantoin (Dilantin) methylphenylethylhydantoin (Mesantoin), methylethylphenyl barbituric acid (Mebaral), and bromides in approximately that order of effectiveness. Such anticonvulsant medication will eliminate the attacks in more than 50 per cent of the cases, and markedly decrease the seizures in another 25 per cent of cases.[7] Thus only 20 to 25 per cent of the focal epilepsies become candidates for surgical intervention.

It would seem foolish to subject an individual to a surgical procedure having a definite risk for the relief of a condition which is of secondary importance to a more crippling ailment. Hence, if the patient is so severely crippled mentally or physically as to render him or her incapacitated, even if the convulsions are eliminated,

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operation is contraindicated. Each case merits a careful evaluation on this point.

When it was demonstrated that electrical stimulation of the cerebral cortex produced clonic movements resembling the motor aura of an epileptic seizure, it was a natural, although not entirely logical, assumption that a cortical lesion was responsible for a focal epilepsy. Upon this hypothesis has been based the treatment of focal epilepsy by cortical excision.

CRITERIA FOR FOCAL EPILEPSY

The focal nature of an epilepsy may be suggested by the clinical history, the electroencephalogram, and angiogram, but only established by the critical examination of the entire clinical picture as colored by the results of the various diagnostic tests.

History.—Hereditary epileptic trends in the family stock may indicate that genetic factors are more important than environmental. A careful inquiry of the patient's birth and early infancy may elicit factors influencing cerebral development or causing brain damage. Statistically, the factors responsible for cerebral lesions vary depending upon the age of the individual at the time of onset of the attacks. In infancy, birth trauma, cerebral anoxemia, and degenerative conditions are common; in childhood, vascular lesions, trauma, and infections; in adolescence, trauma; in young adult life, trauma; in middle age, neoplasm and trauma; and in old age, vascular disease and neoplasm. However, one of these factors may have been present many years before the onset of seizures, so that a birth injury may not cause convulsions until adult life.

Thus, from the past history suggestive evidence of a focal epilepsy may be derived but more direct evidence may be obtained from an accurate "play by play" account of several of the patient's seizures. If the patient cannot describe his attacks or does so vaguely, a relative who has witnessed one or more may be able to give a detailed account. The mode of onset is particularly important since it often gives a clue to the location of the initial neuronal discharge. The occurrence of a postictal paralysis is likewise of localizing significance. If an accurate account cannot be obtained, it may be advisable or necessary to bring on an attack by intravenous injection of Metrazol. Such evoked seizures have all the characteristics of a spontaneous one, and being brought on under strict medical supervision, have little attended risk. During the induction, an electroencephalogram may be made, so that both the clinical and electrical progress may be observed.

Electroencephalograms.—The application of the electronic tube to neurophysiology has made possible the amplification of the minute electrical potentials which accompany neural activity. By this means, it has been possible to record the changes which occur within various parts of the brain from moment to moment. Whereas normal neuronal function is associated with even rises and falls in potential-producing sinusoidal waves on moving paper, convulsive activity is accompanied by rapid fluctuations of electrical potential giving the appearance of a series of spikes.

Many patients suffering from convulsive disorders have alterations in their electroencephalograms between

their actual seizures. Those epileptic individuals with cortical damage usually have localized electroencephalographic alterations in the form of a slow wave focus with or without spiking. Not infrequently, more complex abnormalities are present locally or generally, but commonly with some evidence of a focal origin.[2] Those epilepties suffering from idiopathic, genuine, subcortical epilepsy have in the majority of cases generalized irregularities in the electroencephalogram which may take the form of spike and dome patterns, diffuse spiking, generalized slow cortical activity, or a generally disorganized tracing. Such a n electroencephalographic finding may be present in patients having clinically focal attacks and is an indication of a general neuronal disorder; these cases should be considered idiopathic rather than symptomatic epilepsy and hence unsuitable candidates for cortical excision. On the other hand, some patients having generalized attacks without any focal manifestation may have an electroencephalographic focus. If the latter may be correlated with a previous head injury or other cerebral damage or a lesion demonstrated by pneumoencephalography or angiography, the case may safely be considered a symptomatic epilepsy, for it is known that 25 per cent of known post-traumatic epileptics have attacks without aura.[8] The lesions in such patients are usually in the frontal or temporal lobes.

This poses the question as to the reliability of spiking as an indicator of an epileptogenic zone in the absence of clinical, roentgenological, or pneumoencephalographic evidence of cerebral pathological change. This is a problem which is not yet settled. There is ample evidence that spiking may occur in certain parts of the cortex (temporal lobe), presumably as a normal phenomenon, that it may be present in the cortex as the result of propagation from other cortical areas or subcortical structures, and finally that in idiopathic epilepsy spike foci may wander about the cortex. These observations have cast doubt on the value of spiking as an indicator of an epileptogenic focus in the absence of other clinical or pathological findings. Similarly, a focal convulsion does not necessarily imply that the epileptogenic focus is in the cerebral cortex. Practically 25 per cent of focal epilepsies are associated with diffuse or synchronous dysrhythmic electronencephalographic alterations. One patient suffering from glomerulonephritis and uremia had convulsions beginning with turning of the head and eyes to the right, twitching of the right arm, and then a generalized seizure. It must not be assumed, then, that focal epileptic manifestations necessarily indicate gross focal cortical damage. Nor is it true that the presence of a pathological lesion of the brain demonstrable by roentgenography or surgery necessarily means that it is the epileptogenic factor. A generalized dysrhythmia may indicate a more basic convulsive component. The importance of a single finding or test must depend upon its compatibility with the entire clinical picture.

Knowing the type of seizure, the electroencephalographer can apply his electrodes to the scalp so as to bring out abnormalities which might be associated with the seizure. Thus a history of psychomotor seizures would

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suggest the possibility of a temporal lobe focus, and beside the routine leads, electrodes would be placed in the nasopharynx, the ear, and on the zygoma. Because the abnormalities associated with psychomotor seizures are readily brought out by sleep,[1] after the routine electroencephalogram, the patient might be given Seconal by mouth or Pentothal intravenously to induce narcosis. In other types of focal epilepsy, Metrazol activation[3] may be helpful. With adequate information at his disposal, the electroencephalographer can supply invaluable information, which may confirm a clinical diagnosis.

Roentgenograms of the Skull.—Roentgenograms of the skull may indicate previous trauma, congenital dysplasias of the skull, intracerebral calcifications or erosion of the skull, but, in general, the x-ray findings are less valuable and less often positive than the electroencephalographic findings.

Pneumoencephalograms.—A study of the ventricular and subarachnoid systems may confirm a suspicion of brain damage even in the absence of abnormal clinical signs. If surgical intervention is contemplated, a knowledge of the size and shape of the cerebral ventricles may be of assistance in planning a cortical resection (Fig. 1).

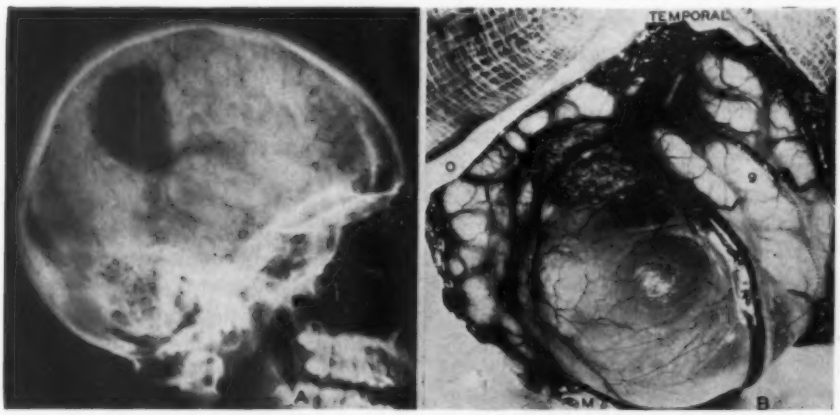

Fig. 1. *A*, Lateral pneumoencephalograms showing a large cortical cyst, and *B*, its appearance at operation, in a patient having focal epilepsy. 9 is the point from which flexion of the right arm was obtained. The extent of the cortical resection at the margin of the cyst is indicated by the dotted line.

Angiography.—Occasionally, an angiogram will reveal unexpectedly a lesion which may be responsible for convulsive seizures. It is a valuable examination in cases suspected of a focal epilepsy.

With the clinical history, the accurate account of the seizures, the electroencephalogram, the roentgenograms of the skull, the pneumoencephalogram, and the cerebral angiograms, it is usually possible to arrive at an anatomical localization of the epileptogenic focus. If a discrepancy between these various examinations becomes apparent, the possibility that

two foci exist must be considered or the likelihood of the condition being an idiopathic rather than a focal epilepsy should be entertained. Only by careful correlation of all of these can a rational conclusion be made of the focal nature of the epilepsy.

The following three cases will illustrate the application of these principles and the types of surgical procedure employed.

Fig. 2 (Case 1).—Photograph of the exposed cerebral cortex to show the arachnoidal thickening and extent of the subpial resection. Responses were obtained to electrical stimulation as follows: 7, flexion of right hand, 9, extension right thumb: "shocks" in right hand. The area of resection is circumscribed by the dotted line.

CASE REPORTS

CASE 1.—D. S. (History No. 333856), a 15-year-old schoolboy, was admitted to the Johns Hopkins Hospital on Nov. 25, 1947, complaining of convulsive seizures and weakness of the right arm and leg since birth. The patient was the third child of his parents and was born spontaneously after an 8-month gestation. Within a few months, the parents became aware of a right-sided hemiplegia. His development proceeded normally, and his hemiplegia gradually improved so that he walked with only a slight limp. In January, 1944, he had his first convulsion while sleeping, following which the attacks have recurred at regular intervals of a few months.

The attacks were, in general, stereotyped, but apparently abortive episodes occurred at times. The attack was initiated by a feeling of dizziness followed by turning of his head to the right and tonic flexor contractions of the right hand and arm. During this period the patient was able to hear people talking but could not see them nor speak himself. The convulsion then became generalized and consciousness was lost. After the attack, the right arm and leg were numb and weak, and the patient was confused.

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The patient's general physical examination was not significant except for aplasia of the right arm and leg. The circumference of the arm, forearm, and leg was 2.0 cm. less on the right than on the left side. The cranial nerves were in order. A right spastic hemiparesis with exaggerated reflexes and an extensor plantar response was noted. The right arm was awkward and slightly ataxic. No sensory disturbances were apparent.

Roentgenograms of the skull were reported as normal. On pneumoencephalography, the left ventricular system was somewhat larger than the right. An electroencephalogram made in 1944 was reported as having random slow waves; one on Dec. 3, 1947, as being generally dysrhythmic. On the latter occasion, 6 c.c. of a 10 per cent solution of Metrazol were given intravenously over a period of eighteen minutes. One minute after the last 2 c.c. were given, 3 per second activity started in the left frontal region and rapidly became generalized as a seizure developed. The electroencephalographer's (Dr. C. Marshall) impression was an epileptogenic focus in the left frontal region.

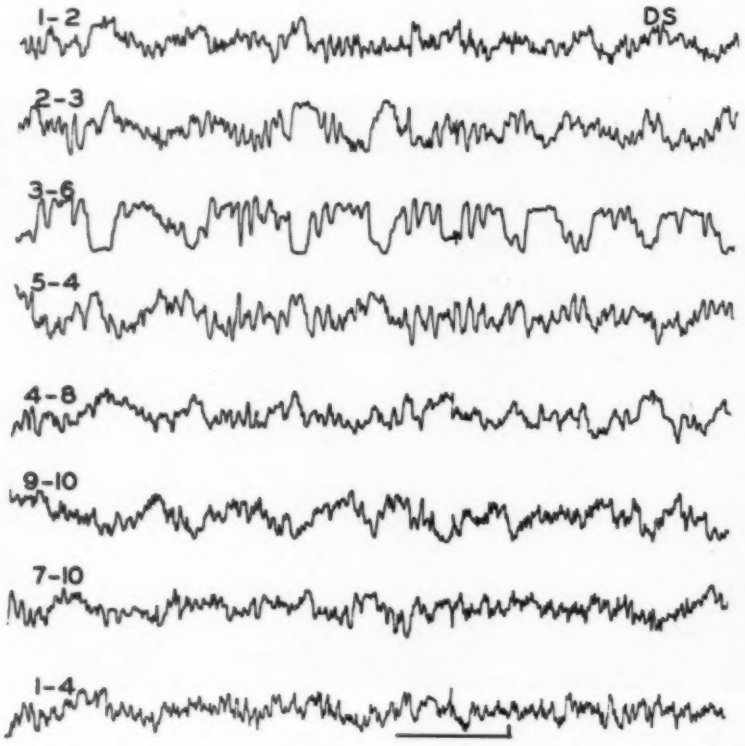

Fig. 3 (Case 1).—Electrocorticogram showing spiky activity particularly marked in the third and fourth traces. The figures correspond to the electrode placements in Fig. 1. The horizontal line at the base indicates an interval of one second; the vertical line a calibration of 50 microvolts.

On the basis of the clinical history, of a right hemiparesis, attacks beginning in the right arm, and a right frontal electroencephalographic epileptogenic focus, an exploration of the

left frontal lobe was advised. On Dec. 5, 1947, after anesthetizing the scalp along the line of the proposed incision, a large osteoplastic flap was reflected. The dura mater was then incised and turned upward. The cortex did not appear abnormal but there was a marked thickening of the arachnoid over the sulci in the frontal region (Fig. 2). An electrocorticogram was made. From an area in the inferior precentral convolution, spiky activity was seen (Fig. 3). Although an active focus could not be located by electrical stimulation and the patient's attacks could not be accurately reproduced, due to the fact that this area corresponded to the region just in front of the hand area which was accurately delimited by the electrical current, it seemed likely that it was responsible for the attack. A subpial dissection was then carried out leaving intact the vascular supply. Replacement of the electrodes was carried out until the spontaneous spiking activity was completely eliminated. At the conclusion of the operation, the electrocorticogram looked very quiet and there was no evidence of spiking spontaneous activity. The dura mater was then closed, the bone flap replaced, and the button of bone in the superior frontal region was put back. The scalp margins were then approximated.

The patient's convalescence was quite stormy due to the slow formation of an extradural clot for which a secondary craniotomy was performed. He gradually improved but it was a month before he talked and was able to walk. At the time of discharge on Jan. 16, 1948, he had marked weakness of his right hand and arm, which were spastic. The right leg was slightly weak and he had a bilateral foot drop. The tendon reflexes and sensation were normal throughout. The patient was advised to take phenobarbital, 1 gr. twice a day.

He has been seen upon numerous occasions since discharge. His general condition rapidly improved although the right hand remained awkward and stiff. He returned to school and did well in his studies.

Until April, 1949, he had no convulsions, although he did not take his medication faithfully. Then he began to have attacks every two to three months. His medication was increased to Dilantin, 1½ gr. at night and phenobarbital, 1½ gr. three times a day.

An electroencephalogram in April, 1949, was reported as showing slight depression of right occipital voltages and fast right central waves—much improved over the previous records.

CASE 2.—E. W. (History No. 447903), a 12-year-old boy, was admitted to the Johns Hopkins Hospital on Jan. 9, 1948, with the complaint of persistent convulsive seizures and behavior disturbances. He had a normal birth, but at the age of 8 weeks had several generalized convulsions. These attacks recurred daily but gradually decreased in frequency. Following a mild head injury at the age of 4 years, they became frequent again. After a particularly severe bout of seizures, the patient developed difficulty in talking and weakness of the right arm and leg. The strength gradually increased and the attacks became less frequent. In October, 1947, he began to have frequent attacks. Anticonvulsant medication did not decrease the attacks, and at the time of admission, in spite of daily doses of Dilantin 0.3 Gm. and phenobarbital 0.24 Gm., the patient was having eight to twelve attacks every day.

The first attacks were generalized without focal phenomena, but the later attacks had been unilateral. The mother stated that the seizure was mainly on the left side, but an attack induced by Metrazol was initiated by turning the head and eyes to the right and predominantly right-sided tonic movements.

For several months before admission, the boy had been unruly, pug-

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nacious, and almost impossible to control. He fought and kicked when an attempt was made to examine him in the hospital, making it necessary to sedate him heavily. No significant abnormalities were noted on general physical examination. The neurological examination was carried out with difficulty as the patient was uncooperative and drowsy. The cranial nerves appeared to be in order except for a bilateral internal strabismus.

On Jan. 16, 1948, the patient was anesthetized with intravenous pentothal. A left occipital bone flap was turned down and the cortex of the occipital lobe inspected. No abnormality was seen. Cortical electrodes were applied and the spontaneous activity sampled. The anterior portion of the exposed cortex had a normal activity but spiky waves were present posterior to electrodes IV and VI. The electrodes were then grouped about

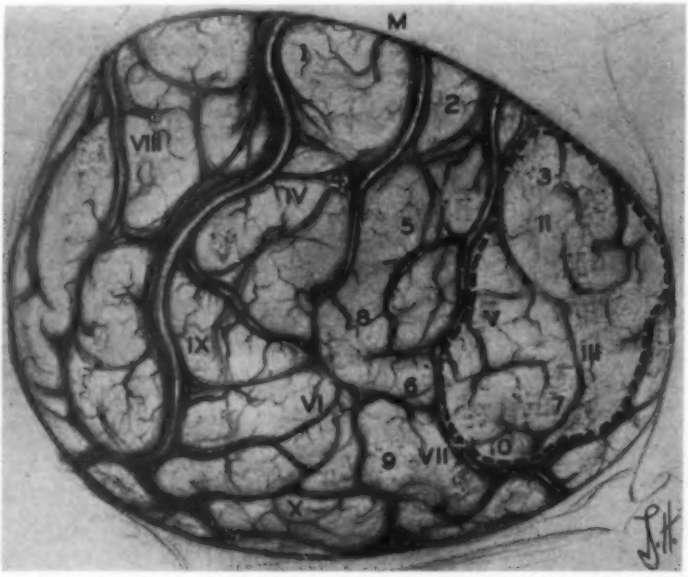

Fig. 4 (Case 2).—Sketch of the exposed cortex of the left occipital lobe. The midline is superior, the occipital pole to the right. The Roman numerals refer to the primary electrode settings, and the Arabic to the secondary setting from which the traces in Fig. 5 are made. The dotted line indicates the site of ablation, but a subpial resection was made anteriorly under points *2*, *4*, and *5*.

As compared to the left, the right arm was generally weak. The reflexes and sensation were normal. Roentgenograms of the skull were not significant. Routine electroencephalograms were reported by Dr. Curtis Marshall as follows: "Basal record shows delta activity in all leads. There is severe spiking in the left occiput. Very severe left occipital spike focus." An examination of the spinal fluid was normal in all respects. A pneumoencephalogram was reported as normal.

this abnormal area as indicated in Fig. 4 by the Arabic numbers and another recording made. The upper two-thirds of the area outlined by the dashed line in Fig. 1 was then removed en bloc. Reapplication of the electrodes about the ablation established further spiking at points *2*, *4*, and *5* which were then removed by subpial dissection. At the conclusion of the procedure, the cortical activity consisted of slow waves without spiking (Fig. 5). The dura mater was

closed and the bone flap replaced, being held in position by one tantalum wire suture.

The patient made a rapid recovery. In the first four days he had one or two rather minor attacks but the seizures then stopped and the patient has been free of attacks since that time, approximately twenty-six months. His behavior has improved, and his mother states that he is getting along well at school and at a boys' club. When last seen he presented no neurological abnormalities. His electroencephalogram was reported as having depressed left-side voltages with fast activity: on hyperventilation there was slowing to 3 per second.

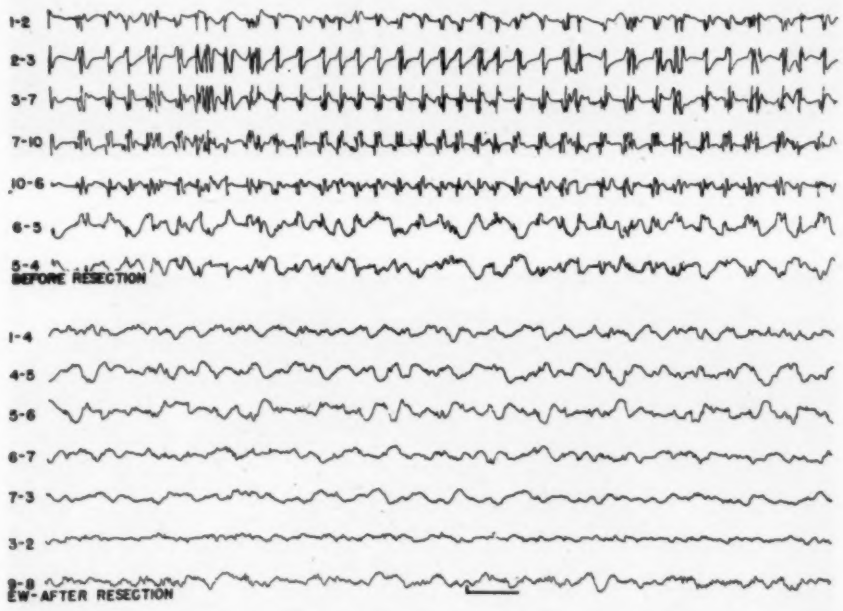

Fig. 5 (Case 2).—Electrocorticograms showing the spontaneous electrical activity before and after resection of the epileptogenic focus. The electrode placements are indicated in Fig. 4.

Case 3.—M. A. (History No. 521675), an 11-year-old boy, was admitted to the Johns Hopkins Hospital on Nov. 23, 1949, because of uncontrollable convulsive seizures. He was born spontaneously at term after a twenty-eight-hour labor. He fed poorly, and thirty-six hours after delivery had a generalized convulsion. During the next fourteen days in hospital he had about 100 convulsions. He required tube feeding and a transfusion. He walked just before the age of 2 years; said words about the same time and sentences at 4 years of age.

At about 2 years of age, the patient had a generalized convulsion and was in coma for five days. Since that time he has had at least one generalized tonic clonic convulsion every day in spite of all medication. On December 3, 1949, he had a right central craniotomy and is said to have had a blood clot removed from his brain.

The patient has never gone to school because of his mental retardation but he has had tutors. He has always had a weakness of the left extremities.

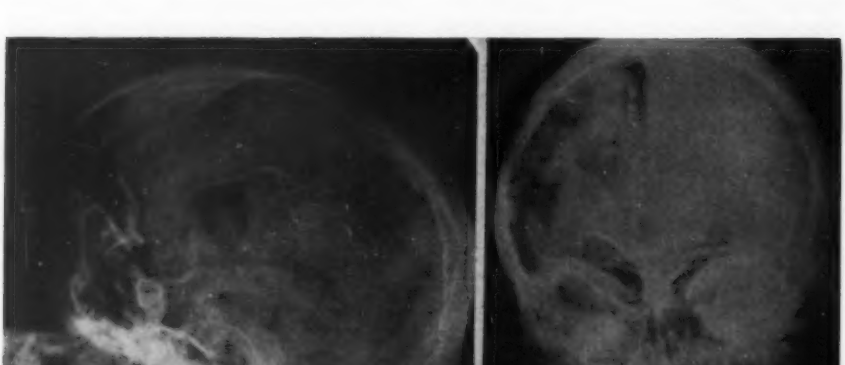

Fig. 6 (Case 3).—Lateral (*A*) and occiput down (*B*) pneumoencephalograms showing the marked atrophy of the right cerebral hemisphere.

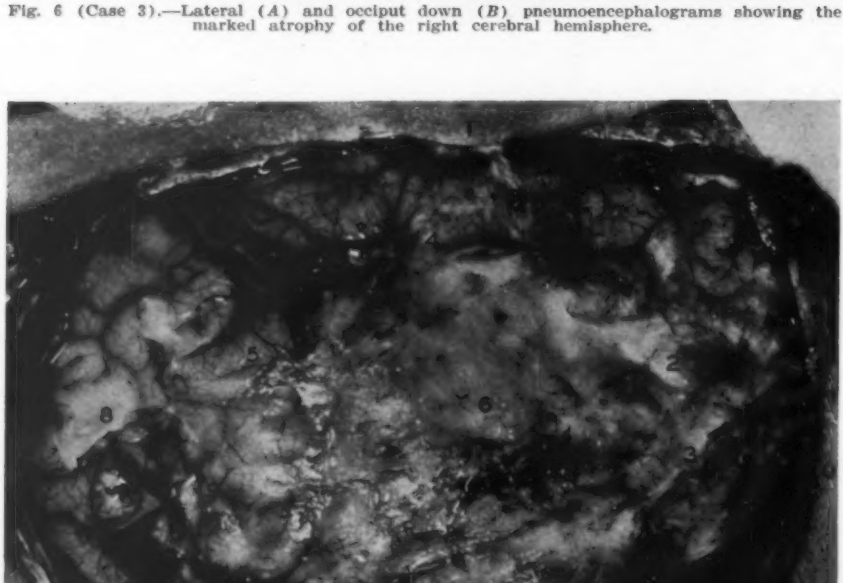

Fig. 7 (Case 3).—Photograph of the exposed brain showing the severe cortical scarring and the position of the cortical electrodes.

The patient was a hirsute, dark lad who refused to cooperate in any type of examination. His general physical examination was not significant except for atrophy and contractures of the left extremities and slight genital enlargement.

Although the boy spoke Spanish and a little English, he could not read. He was able to indicate how to use objects such as a pair of scissors, comb, or cigarette.

He had no disturbance in the cranial nerves.

The left arm and left leg were atrophic and shortened. The left hand assumed an athetoid posture and the left leg a pes equinus due to marked shortening of the tendo Achilles. When the right hand was moved, there were athetoid movements of the left hand. The left extremities could be moved at the large joints but usually in association with some movement of the right limbs. Fine movements could not be performed with the left extremities which were markedly spastic. All the left tendon reflexes were markedly exaggerated but both plantar reflexes were flexor.

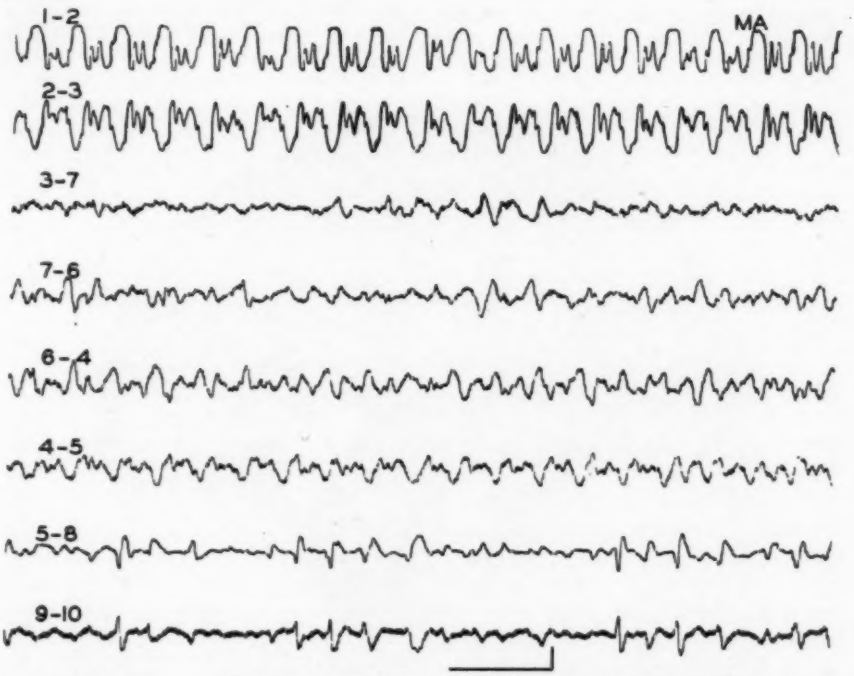

Fig. 8 (Case 3).—Spontaneous electrocorticogram showing the generalized spiky activity and localized seizure. The electrode placements are shown in Fig. 7. The horizontal line at the base indicates an interval of one second; the vertical line a calibration of 200 microvolts.

There was a well-healed scar in the right frontoparietal region.

A combined pneumoencephalogram was made on Nov. 26, 1949. The right cerebral hemisphere was much smaller than the left and the sagittal fissure was to the right of the midline (Fig. 6).

The ventricles were large and there was considerable air over the surface of the brain in dilated sulci. The right cerebral vessels appeared quite small but there was no displacement.

On Dec. 2, 1949, the patient was anesthetized with ether. A large incision was made well outside of the previous central incision. A large bone flap was made exposing practically the entire right cerebral hemisphere. This was accomplished with very little difficulty. The longitudinal sinus posteriorly was exposed and a small strip of Gelfoam had to be placed over it in order to obtain hemostasis. The dura mater was then elevated. It was not adherent to the underlying brain except at the site of the former craniotomy where there were numerous rather dense adhesions (Fig. 7). The cortex was then explored by electrocorticography. There were spontaneous spike discharges both anteriorly and posteriorly (Fig. 8). The motor area could not be accurately defined by the stimulating electrodes. Accordingly, the middle cerebral artery was clipped deep in the Sylvian fissure, the veins were coagulated as they passed into the lateral and longitudinal sinus, and the entire hemisphere was then separated from the corpus callosum and turned laterally. The cortex was cut along the inferior surface of the frontal lobe and the inferior part of the temporal lobe. This exposed the insula, which was removed. After complete hemostasis, the dura mater was closed and tacked up to the pericranium. The bone flap was put back in place and held with two tantalum sutures.

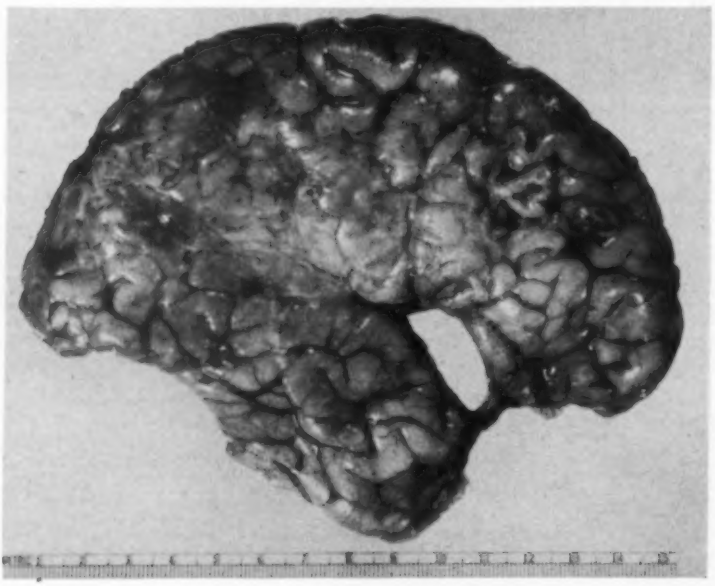

Fig. 9 (Case 3).—Photograph of the ablated hemisphere.

The specimen consisted of the right cerebral hemisphere which measured approximately 12 × 14 × 3 cm. and weighed 193 grams. The frontal, parietal, and temporal lobes appeared intact. Over the entire Sylvian region extending into the parietal lobe, the leptomeninges were thickened and milky. The blood vessels in this same area were small, atrophic, and few in number. The convolutions of the entire hemisphere were markedly narrow and atrophic (Fig. 9).

The patient recovered consciousness about three hours after the hemispherectomy. He was able to move the left arm voluntarily synchronously with the right one. He appeared to appreciate pain on both sides of his face. The tendon reflexes were present on the left side but there was no Babinski response. The patient vomited occasionally on the first two postoperative days but then kept all food down.

Eight days after operation the patient had an attack in which the left arm drew up and the fingers writhed, and there were several myoclonic jerks of the head to the left. During the next two weeks he had numerous myoclonic jerkings while asleep and one episode of status epilepticus for ten minutes. All attacks occurred during sleep. The boy walked about unaided within a month postoperatively.

At the time of discharge seven weeks after his hemispherectomy, the patient was much more cooperative and less resistant to examination. He still became noisy upon awakening in the morning. He had had only four to five myoclonic jerkings during the last week of his hospital stay and had had no generalized attacks for one month. His neurological status was essentially as it had been at admission. The patient's mother said that, so far as she could see, he was able to do everything that he could before operation. In particular, the movements of the left extremities were as good as at the time of admission.

Four months after the patient's operation, his mother stated that he had had no attacks during the day. In his sleep he had a generalized seizure about once a week, and minor episodes consisting of drawing up of the left arm almost every night. He talked and walked much better than before his hemispherectomy. Even his unruly behavior was improved although he was spoiled and demanded attention.

DISCUSSION

These three cases illustrate the surgical techniques which may be employed for focal epilepsy. In all cases the focal nature of the seizures could be established by clinical history and examination as well as electroencephalography. Pneumoencephalographic and angiographic evidence was corroborative in two cases.

The type and extent of cortical extirpation necessary to eliminate the epileptic focus vary greatly. In Case 1, subpial resection of the focus was adequate and should produce minimal scarring. In Case 2, in which the epileptogenic zone involved a large area at the occipital pole, a partial occipital lobectomy was necessary. In the child with infantile hemiplegia, a hemispherectomy was required to eliminate the abnormal scarred tissue. In planning a resection, it is essential to avoid increasing the disability of the patient. In post-traumatic conditions, it is surprising how much atrophic scarred tissue may be resected without impairing further the strength of hemiplegic limbs and in some cases with actual improvement of the mental and physical status of the child.

The end results of surgical treatment cannot be assessed accurately until cases have been followed for a period of at least five years. Because present electrocorticographic techniques have only been in use slightly longer than that time, a large series of children treated by these methods is not available. Many isolated cases have been reported with good results for relatively long periods of time. Such reports have emphasized the physical and mental improvement

which may follow surgical resection of epileptogenic foci.[5]

If one may assume that the results in children would be similar to those obtained in adults,[6] slightly more than 50 per cent of the patients should be relieved or almost relieved of attacks and another 25 per cent improved. Since surgical extirpations are made only when medical management has failed, these results must be considered satisfactory. They should be bettered as the diagnostic and surgical techniques improve. But even now, cortical excision of an epileptogenic focus offers considerable promise to a group of patients otherwise considered incurable.

SUMMARY

1. Surgical treatment for focal epilepsy should be considered when medical management has failed.

2. The focal nature of an epilepsy may be suggested by the clinical history, the electroencephalogram, pneumoencephalogram, and angiogram, but only established by the critical examination of the entire clinical picture colored by the results of the various diagnostic tests.

3. Three cases are presented illustrating the various types of cortical resections for focal epilepsy.

4. Depending upon the extent of the focus, subpial resection, partial lobectomy, or hemispherectomy may be necessary to eliminate the abnormal activity.

5. The results offer promise to a group of focal epilepsies otherwise considered incurable.

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DETERMINATION OF SODIUM^{24} "SPACE" IN INFANTS, CHILDREN, AND ADULTS*

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INTRODUCTION

STUDIES of the apparent volume of distribution of radioactive sodium^{24} in man (sodium "space") have been made by a number of investigators. Kaltreider, Meneely, Allen, and Bale[1] in 1941 reported observations on the fluid available for the distribution of Na^{24} over periods of 3, 6, 9, and 12 hours, and applied certain corrections to the 6-, 9-, and 12-hour values for exchange of Na^{24} with excess sodium in the skeleton. Sulfocyanate space was determined simultaneously. Moore[2] in 1946 reported measurement of the various fluid compartments in man by the isotopic method, giving a single value for radio-sodium volume in an adult. The period allowed for distribution was not stated. Flexner and associates[3] measured sodium space in three newborn infants 2½ to 3 hours after injection of Na^{24}. Changes in thiocyanate and sodium spaces during growth were reported by Fellers, Barnett, Hare, and McNamara[4] in 1949. They observed the sodium spaces occupied between 2½ and 4 hours after injection of the Na^{24} in thirty-two infants and children and in five adults.

In this paper we are reporting estimations of the fluid through which Na^{24} is rapidly distributed (sodium "space") in nineteen adult males and thirty-seven infants and children, and have extended the observations to smaller premature infants than those hitherto reported. The measurements were made from 1¾ to 4½ hours after intravenous injection of the Na^{24}.

METHODS

Most of the infants studied were healthy newborn babies in the St. Louis Maternity Hospital. The remaining infants and the older children were patients on the wards of the St. Louis Children's Hospital and were free from cardiac, renal, or allergic diseases. Their general nutritional and physical condition was good. None of them was receiving fluid therapy. The adult subjects included medical students and members of the resident house staff. They were all in good health.

Radioactive Na^{24}, half-life 14.8 hours, was prepared in the Washington University cyclotron by deuteron bombardment of metallic sodium; in our laboratory the material was converted to the chloride, and sufficient water was added to render the solution isotonic. It was then autoclaved and diluted with sterile saline to the proper activity. The material was injected intravenously, using the method described by Barnett and Fellers[5]

From the Department of Pediatrics, Washington University School of Medicine; the St. Louis Children's Hospital, and the St. Louis Maternity Hospital.

The cooperation of the Cyclotron Group at Washington University is gratefully acknowledged.

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**Fellow of the American College of Physicians during the period of this study.

TABLE I. SODIUM "SPACE" IN INFANTS AND CHILDREN

SUBJECT	SEX	AGE	WEIGHT (KG.)	TIME AFTER INJECTION	NA "SPACE" PER CENT BODY WT.
Fo.	M	22 da.	1.70	2 hr. 50 min.	51.5
He. B.	F	7 da.	1.87	3 hr. 0 min.	43.2
He. A.	F	7 da.	1.87	3 hr. 26 min.	44.8
Da.	M	16 da.	1.98	2 hr. 14 min.	39.3
Do.	F	15 da.	2.04	3 hr. 9 min.	48.7
Pe.	F	15 da.	2.12	2 hr. 51 min.	49.9
McCr.	M	15 da.	2.33	2 hr. 49 min.	43.7
We.	F	4 da.	2.34	3 hr. 20 min.	49.8
Tr.	M	21 da.	2.42	2 hr. 0 min.	36.5
Fr.	M	4 da.	2.43	3 hr. 23 min.	33.2
Be.	M	5 da.	2.48	3 hr. 28 min.	38.0
Al.	F	6 da.	2.52	2 hr. 38 min.	39.6
Is.	F	5 da.	2.57	3 hr. 31 min.	33.8
Th.	M	7 da.	2.57	1 hr. 50 min.	41.3
Mi.	F	8 da.	2.61	2 hr. 48 min.	38.5
Ca.	F	1 da.	2.89	1 hr. 40 min.	35.5
Ra.	M	4 da.	3.02	1 hr. 58 min.	33.2
Gl.	M	3 da.	3.02	4 hr. 17 min.	34.6
Br.	M	3 da.	3.06	4 hr. 25 min.	39.6
Ad.	M	3 da.	3.17	4 hr. 29 min.	39.2
Bl.	M	7 da.	3.18	3 hr. 18 min.	31.1
Ma.	M	6 da.	3.23	3 hr. 19 min.	34.4
Bo.	M	2 da.	3.25	2 hr. 10 min.	34.0
Ha.	M	3 da.	3.35	3 hr. 35 min.	28.2
Pa.	F	16 hr.	3.37	1 hr. 44 min.	32.8
Lu.	F	13 wk.	3.65	2 hr. 6 min.	40.0
Sp.	F	6 da.	3.78	2 hr. 39 min.	35.6
Av.	M	8 da.	4.57	2 hr. 13 min.	33.4
E. H.	M	10 wk.	4.86	2 hr. 15 min.	43.4
R. S.	M	10 wk.	6.00	2 hr. 10 min.	32.5
G. J.	M	14 mo.	6.96	3 hr. 17 min.	35.2
S. P.	F	13 mo.	9.45	2 hr. 59 min.	27.9
S. McF.	M	22 mo.	11.6	2 hr. 58 min.	23.2
E. R.	M	3 yr.	15.4	2 hr. 19 min.	33.8
B. T.	M	3½ yr.	18.4	1 hr. 48 min.	31.4
C. M.	F	10 yr.	23.9	2 hr. 26 min.	31.3
L. McK.	M	14 yr.	56.8	2 hr. 44 min.	28.9

for the quantitative administration of small volumes of fluid. The volume of Na^{24} solution injected was usually 1.0 c.c., rarely 2.0 c.c., and the volume of wash solution was 3 c.c. The quantity of Na^{24} given to these subjects ranged from 1 to 1½ microcuries per kilogram of body weight; this amount has been computed to deliver a total dose of from 0.11 to 0.17 roentgens equivalent physical in the adult.[6]

Venous blood samples were drawn, at the times to be stated, from a vein other than the one used for the injection. The serum was separated from the clot within one hour after collection. One cubic centimeter amounts of serum, usually in duplicate, were transferred to metal planchets,* 33 mm. in diameter containing a drop of "acidolate" to facilitate spreading, and the samples were dried in the oven at 70° to 80° C. Suitable aliquots of the Na^{24} solutions were prepared in the same way in duplicate or triplicate. Urine samples were prepared similarly. An end window Geiger tube with autoscaler was used in measuring the activity. The counting periods for most of the serum

*In the earlier studies, watch glasses or porcelain capsules were used for mounting the samples.

TABLE II. SODIUM "SPACE" IN ADULT MALES

SUBJECT	AGE (YR.)	WEIGHT (KG.)	TIME AFTER INJECTION	PER CENT ADMINISTERED NA^{24} EXCRETED DURING DISTRIBUTION PERIOD	NA "SPACE" PER CENT BODY WT.
H. M. (1)	29	58.3	3 hr. 11 min.	1.1	19.7
H. M. (2)	29	60.6	3 hr. 40 min.	2.3	27.4
W. D.	28	66.2	3 hr. 0 min.	1.2	26.4
D. B.	22	67.3	3 hr. 2 min.	0.3	27.1
W. G.	25	68.1	2 hr. 52 min.	0.3	35.8
B. H.	25	71.8	3 hr. 36 min.	0.2	21.5
M. C.	23	71.8	3 hr. 15 min.	1.2	24.1
R. B.	24	73.5	3 hr. 41 min.	1.3	20.6
R. B.	28	73.9	3 hr. 17 min.	1.3	26.1
J. Mc.	24	73.9	3 hr. 30 min.	1.6	25.8
S. S.	25	74.1	3 hr. 30 min.	0.4	28.6
L. K.	27	74.4	3 hr. 0 min.	1.0	25.4
R. M.	23	75.6	3 hr. 43 min.	1.8	27.4
R. G.	24	75.4	2 hr. 45 min.	0.8	30.5
V. T.	34	75.4	3 hr. 30 min.	1.3	20.8
A. R.	26	77.6	3 hr. 0 min.	2.1	27.6
J. R.	29	77.8	3 hr. 0 min.	1.2	24.4
P. J.	24	84.8	3 hr. 44 min.	0.6	20.2
A. H.	28	91.6	3 hr. 16 min.	0.9	23.5
E. C.	23	100.0	3 hr. 46 min.	1.7	20.8
Average				1.1	25.2

TABLE III. SUMMARY OF SODIUM "SPACE" IN INFANTS, CHILDREN, AND ADULTS

RANGE OF WEIGHT (KG.)	NO. SUBJECTS	RANGE OF NA "SPACE" PER CENT OF BODY WT.	MEAN
1.70- 1.98	4	39.8-51.5	44.8
2.04- 2.48	7	33.2-49.9	42.8
2.52- 2.89	5	33.8-41.3	37.7
3.02- 3.78	11	28.2-40.0	34.8
4.57- 6.96	4	32.5-43.4	36.1
9.45- 18.4	4	23.2-33.8	29.1
23.9 - 56.8	2	28.9-31.3	30.1
58.3 -100.0	19	19.7-35.8	25.2

samples were of such length that the statistical variation due to random fluctuations of radioactive emission was ±3 per cent or less (standard deviation).

The volume of distribution of Na^{24} at any given time was computed by dividing the quantity of the Na^{24} injected (corrected for urinary loss during the period of equilibration in the case of adults) by the quantity in 1.0 c.c. of serum. Correction was not made for the Donnan effect, for the water content of the serum, or for the volume of fluid injected when the Na^{24} was given.

RESULTS

The values for sodium "space" in thirty-seven infants and children ranging in age from 16 hours to 14 years are given in Table I. They varied from 23.2 to 51.7 per cent of body weight. The results of twenty determinations on nineteen adult males from 22 to 34 years of age are to be found in Table II. The sodium "space" ranged from 19.7 to 35.8 per cent of the body weight and averaged 25.2 per cent. A summary of the values for the different weight ranges is given in Table III. The values for sodium "space" for all the

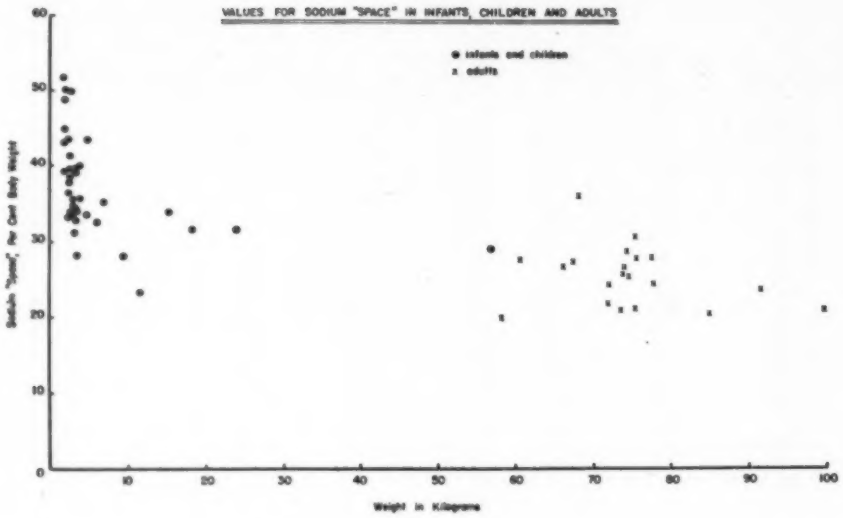
VALUES FOR SODIUM "SPACE" IN INFANTS, CHILDREN AND ADULTS
• infants and children
x adults
Sodium "Space", Per Cent Body Weight
Weight in Kilograms
0
10
20
30
40
50
60
70
80
90
100

Fig. 1.

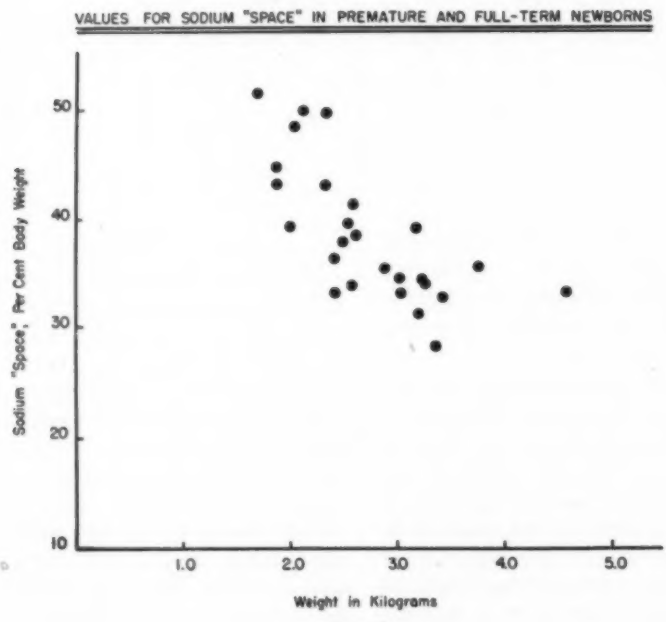
VALUES FOR SODIUM "SPACE" IN PREMATURE AND FULL-TERM NEWBORNS
Sodium "Space," Per Cent Body Weight
Weight in Kilograms
10
20
30
40
50
1.0
2.0
3.0
4.0
5.0

Fig. 2.

subjects listed in Tables I and II are plotted in Fig. 1. Fig. 2 shows the values for only the newborn infants, including both full-term and premature infants. In the small weight range covered here, striking differences are to be seen in the sodium "space." The highest values with respect to weight occur in the very small infants.

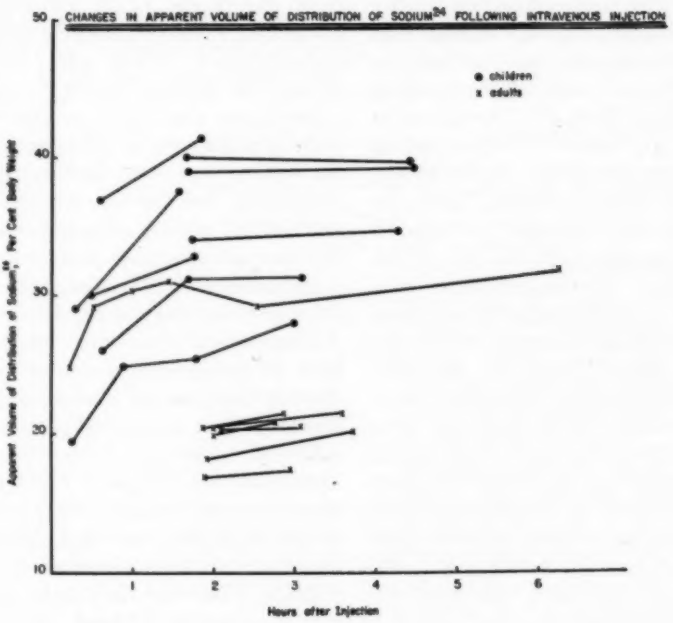

Fig. 3.

DISCUSSION

In determining sodium "space" by the procedure which we have described we have measured the volume of fluid in the body with which sodium exchanges readily, that is, into which and out of which sodium passes rapidly. This determination, however, does not necessarily afford a measure of the volume of extracellular fluid. During the period of time which must be allowed for the distribution of sodium^{24} through the extracellular fluid, there is probably some passage of sodium into non-extracellular compartments, particularly intracellular fluid and bone.[1, 7] On the other hand, sodium is distributed less rapidly through spinal fluid than through other portions of the extracellular compartment, about 12 hours being required for equilibrium to be established between serum and spinal fluid as observed by Kaltreider and collaborators.[1] These authors also postulate that sodium may penetrate comparatively slowly into the extracellular spaces of central nervous system tissue. Manery and Bale also are of this opinion.[7]

The periods allowed for the distribution of Na^{24} in the observations made by other workers have already been mentioned. In our studies on infants and children, the time allowed ranged from 1 hour 40 minutes to 4½ hours. Fig. 3 gives the apparent volume of distribution of Na^{24}, computed as per cent of body weight, plotted against time in a number of subjects from whom two or more blood samples were collected after the injection of Na^{24}. It may be seen that in the infants observed, during the period between 1 and 1¾ hours after the injection, there is a sharp rise in the apparent volume of distribution, but between the latter time and 4½ hours the curves flatten, and the change in the apparent volume is slight, indicating that the end of the rapid phase of mixing has been reached. In four cases the apparent volume increased 0.5 per cent, 1.5 per cent, 0.3 per cent, and 9.1 per cent, respectively, during this time; in a fifth the value decreased 1 per cent. We conclude, therefore, that in infants and children the volume of fluid with which sodium exchanges readily may be approximated at any time between 1 hour 40 minutes and 4½ hours after the Na^{24} has been injected intravenously.

In the adults reported in Table II, the period allowed for equilibration was between 2¾ and 3¾ hours. In Fig. 3 are plotted the apparent volumes of distribution against time in six subjects on whom more than one blood sample was drawn between 1 hour 52 minutes and 3 hours after the injection. The increases in apparent volume amounted to 4.5 per cent, 5.4 per cent, 11 per cent, 2 per cent, 5 per cent, and 2.4 per cent, respectively. In this period of time the apparent volume of distribution of Na^{24} is increasing very little and, therefore, would serve to estimate the volume of fluid available for distribution of readily exchangeable sodium.

In the adult subjects, the excretion of Na^{24} during the period allowed for distribution was measured, and the values may be seen in Table II. The loss after injection, during periods of from 2¾ to 3¾ hours, ranged from 0.3 to 2.3 per cent of the amount given and averaged 1.2 per cent. In computing the sodium "space" in adults, a correction was made for this loss in each instance, but it is apparent that the results are not significantly affected. In the infants and children studied, estimation of and correction for the urinary loss was not made since collection of urine over these short periods was not feasible.

Other methods which have been used in an attempt to measure extracellular fluid in man also have certain disadvantages as pointed out by Kaltreider and associates.[1] Sucrose, while having the advantage of being a nonelectrolyte, is unsatisfactory because it is quite rapidly excreted. The same objection applies to sulfate. Thiocyanate, while rapidly distributed and slowly excreted, diffuses into the red blood cells and into the cells of certain glandular organs. Nevertheless, measurements of the sodium "space" and thiocyanate space provide useful relative values.

Our finding that the sodium "space" computed as per cent of body weight is considerably higher in young infants than in older children and adults confirms the observations of Fellers and co-workers.[4] From Table I it is apparent that the

average sodium "space" in eleven premature newborn infants is higher than in the sixteen full-term newborn infants, being 43.5 per cent of the body weight in the former group and 35.3 per cent in the latter. Harrison, Darrow, and Yannet,[8] using the chloride analyses of Iob and Swanson,[9] have computed "extracellular fluid" contents of fetuses and obtained a value of 62 per cent of body weight on a 5-month fetus with values decreasing to 43 per cent of body weight on one which was practically full term.

Our observations on children from 1 to 14 years of age are too few to bear analysis, but the sodium "spaces" are appreciably lower than those of young infants, averaging 30.2 per cent. Fellers and collaborators[4] observed a period of relative constancy between early infancy and adolescence with a small decline during adolescence. Our sodium "spaces" on adults vary widely as do those of Kaltreider and associates,[1] but the average of 25.2 per cent of body weight compares well with their mean of 24.8 per cent and with that of 27.1 per cent reported by Fellers and coworkers[4] and the single value of 26.5 per cent obtained by Moore.[2]

SUMMARY AND CONCLUSIONS

1. The volume of fluid through which radioactive sodium^{24} is rapidly distributed (sodium "space") has been measured in thirty-seven infants and children and in nineteen adult males.

2. The period allowed for distribution of Na^{24} ranged from 1¾ to 4½ hours.

3. In eleven premature infants the sodium "space" averaged 43.5 per cent of body weight, and in 16 full-term newborn infants 35.2 per cent. In seven children from 1 to 14 years of age, the values averaged 30.2 per cent, and in nineteen adult males 25.2 per cent.

4. Although the sodium "space" computed as per cent of body weight varied considerably in given weight ranges, the data indicate that the volume of fluid occupied by sodium in relation to body weight declines as growth proceeds.

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ILLNESS IN THE FIRST TRIMESTER OF PREGNANCY: ITS LACK OF SIGNIFICANCE IN RELATION TO CONGENITAL ANOMALY OF THE OFFSPRING AND TO FULL-TERM PREGNANCY, PREMATURITY, AND STILLBIRTH*

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THE primary purpose of the study here reported was to determine the relation of illness in the first trimester of pregnancy to the occurrence of congenital anomalies of infants born in 1948 at St. Marys Hospital in Rochester, Minn. Data concerning the mothers were obtained partly from the obstetric records of the Mayo Clinic and partly by means of a questionnaire which was distributed to expectant mothers at their first prepartum visit. The information concerning the infants was obtained from the pediatric records of the clinic. Although 1,480 mothers gave birth to children in St. Marys Hospital in 1948, data concerning the health of certain of the mothers were incomplete. Some mothers had come for their first prenatal visit when pregnancy was well advanced and had forgotten the details of the first trimester. Others had received prepartum care from physicians elsewhere. There remained for inclusion in the study, therefore, 1,228 mothers who gave birth to 1,237 infants. Anomalies were observed in examination of sixty-five infants (5.3 per cent).

For the next few lines, attention will be directed mainly to Tables I to VI, inclusive. A few of the infants had multiple deformities, but only the chief anomaly is recognized in Table I. The sex of the affected children is the subject of Table II. Concerning the health of the mothers, as has been indicated, account was taken only of the first three months of gestation. Throughout these months, mothers whose pregnancies were uneventful numbered 1,080; those with illness of one kind or another, 148 (Table III). No appreciable difference was found between the incidence of congenital anomalies following maternal illness and the incidence following pregnancy uncomplicated by illness (Table III). The highest incidence of congenital anomalies (9.8 per cent) followed maternal illness in the second month of gestation (Table IV). The mothers' illnesses are listed in Table V and their relation to the incidence of anomalies of the offspring is evident. In Table VI, the illness of the mother and the month of gestation when the illness occurred are related to the anomaly of her infant.

Because Miller and Wilson[1] found that 30 per cent of pregnancies of diabetic mothers terminated in stillbirths, or the children died in the

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TABLE I. CHIEF ANOMALIES OF INFANTS

ANOMALY	CASES	MALE	FEMALE
Congenital heart disease	7	2	5
Congenital cataracts	2	1	1
Microphthalmos	1	1	
Anencephaly	1	1	
Hydrocephaly	1	1	
Monstrosity	1		1
Spina bifida	2		2
Omphalocele	2		2
Meckel's diverticulum	1		1
Inguinal hernia	1	1	
Hydrocele	2	2	
Undescended testicles	3	3	
Torticollis	6	2	4
Deformities of feet	10	4	6
Absence of single bones	3		3
Malformation of parietal and occipital bones	1	1	
Hemangiomas	8	1	7
Pigmented nevus	1	1	
Dermoid cyst at angle of eye	1		1
Multiple mesenteric cysts	1	1	
Mediastinal teratoma	1		1
Polycystic kidney	1	1	
Kidney tumor, undiagnosed	1		1
Abdominal tumor, undiagnosed	1	1	
Supernumerary nipple	1		1
Preauricular sinuses	1	1	
Hypermotility of joints	1		1
Generalized muscular weakness	1	1	
Congenital ichthyosiform erythroderma	1	1	
von Recklinghausen's disease	1		1
Total	65	27	38

TABLE II. SEX OF INFANTS WITH ANOMALIES

SEX	NUMBER	PER CENT
Males	27	41.5
Females	38	58.5
Total	65	100.0

TABLE III. MATERNAL ILLNESS IN FIRST TRIMESTER OF PREGNANCY AND ITS RELATION TO INCIDENCE OF CONGENITAL ANOMALIES OF INFANTS

MOTHERS		INFANTS DELIVERED		
			WITH ANOMALIES	
HEALTH	TOTAL	TOTAL	NUMBER	PER CENT
No illness	1,080	1,088	57	5.2
Illness	148	149	8	5.4
Total	1,228	1,237	65	5.3

TABLE IV. RELATION OF MONTH OF GESTATION IN WHICH THE MOTHER WAS ILL TO INCIDENCE OF CONGENITAL ANOMALIES OF INFANTS

MONTH OF GESTATION	MOTHERS	INFANTS WITH ANOMALIES	
		NUMBER	PER CENT
1	69	2	2.9
2	41	4	9.8
3	30	2	6.7
Not stated	8	0	
Total	148	8	5.4

TABLE V. RELATION OF ILLNESSES OF MOTHERS TO INCIDENCE OF ANOMALIES OF INFANTS

DIAGNOSIS	MOTHERS	INFANTS WITH ANOMALIES	
		NUMBER	PER CENT OF NUMBER OF MOTHERS
Acute illnesses:			
"Flu" or "la grippe"	16	2	12.5
Respiratory infection (above throat)	45	2	4.4
Throat infection	13	1	7.7
Pneumonia	2	0	
Otitis media	2	0	
Bronchitis or "chest cold"	11	0	
Sinusitis	7	0	
Mumps	1	0	
German measles	1	0	
Scarlet fever	1	0	
Measles	1	0	
Acute rheumatic fever	1	0	
Rheumatoid arthritis (acute)	1	0	
Gastrointestinal upset	2	1	50.0
Urinary tract infection	7	2	28.6
Appendicitis (rupture)	1	0	
Infectious hepatitis	2	0	
Chronic illnesses:			
Bronchitis	1	0	
Sinusitis	3	0	
Rheumatic fever	1	0	
Urinary tract infection	1	0	
Pulmonary tuberculosis			
active	4	0	
inactive	5	0	
Osteomyelitis	1	0	
Cholecystitis	1	0	
Taboparesis	1	0	
Diabetes mellitus	5	0	
Hyperthyroidism	3	0	
Spontaneous myxedema	1	0	
Multiple sclerosis	2	0	
Other:			
Malignant tumor	2	0	
Convulsive disorder (1 mother included in "flu")	1 (2)	0	
Tinnitus	1	0	
Sepsis. Attempted criminal abortion	1	0	
Total	148	8	5.4

TABLE VI. ILLNESS OF MOTHER, MONTH OF GESTATION WHEN IT OCCURRED AND ANOMALY OF INFANT

MOTHER		
ILLNESS	MONTH OF GESTATION	ANOMALY OF INFANT
"Flu"	2	Malformation of parietal and occipital bones. Equinovarus deformity left foot, grade 2-3
"Flu"	2	Monstrosity
Upper respiratory infection	2	Right forefoot adduction
Upper respiratory infection	3	Marked left metatarsus varus
Throat infection	3	Hydrocephaly suspect
Gastrointestinal upset	2	Carvernous hemangioma on forehead
Urinary tract infection	1	Congenital omphalocele
Urinary tract infection	1	Spina bifida. Imperforate anus

neonatal period, the five mothers of this study who had diabetes commanded particular interest. The pregnancy of one of these mothers terminated in stillbirth at full term. Another child was born after a gestation of seven months and died soon after birth. Neither of the foregoing infants was deformed. The remaining three children all were born at term, were without anomalies, and survived.

Hospital in Rochester, Minn., 148 mothers were ill at some time in the first trimester of pregnancy. These ill mothers subsequently gave birth to 149 children, eight of whom (5.4 per cent) had congenital anomalies. The 1,080 mothers who were not ill in the first trimester of pregnancy gave birth to 1,088 infants of whom fifty-seven (5.2 per cent) had congenital anomalies.

TABLE VII. RELATION OF MATERNAL ILLNESS TO INCIDENCE OF FULL-TERM BIRTHS, PREMATURE BIRTHS, AND STILLBIRTHS

INFANTS DELIVERED	MOTHERS ILL		MOTHERS NOT ILL	
	NUMBER OF INFANTS	PER CENT	NUMBER OF INFANTS	PER CENT
At full term	140	93.9	1,032	94.8
Prematurely	5	3.4	41	3.8
Stillborn	4	2.7	15	1.4
Total	149	100.0	1,088	100.0

The foregoing paragraph entered the field of the secondary purpose of this study, which had to do not with infantile anomaly but with determination of the possible effect of illness of mothers in the first trimester of pregnancy on the incidence of full-term births, premature births, and stillbirths. It is evident in Table VII that the presence or absence of maternal illness apparently was without effect in the respects mentioned.

Thus, there was no significant difference between the incidence of congenital anomalies following maternal illness in the first trimester of pregnancy and that following uneventful pregnancy.

Furthermore, whether or not the mothers were ill in the first trimester of pregnancy apparently made no significant difference in the incidence of full-term pregnancy, prematurity, or stillbirth.

SUMMARY

Of 1,228 mothers who gave birth to 1,237 infants in 1948, at St. Marys

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ERYTHEMA MULTIFORME EXUDATIVUM

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ERYTHEMA multiforme exudativum has been described as an acute inflammatory disease of the skin with constitutional symptoms compatible with an acute infection. The eruption may be erythematopapular, vesiculobullous, or both. Lesions usually start as macules or papules on the dorsa of the hands and spread along the forearms and neck, eventually involving the forehead and face. Spread is similar over the lower extremities. At the height of fever the lesions are generalized. Vesicles and bullae form when sufficient exudate occurs in the original lesions. Pustules are secondary to superimposed infection.

Lever[1] has stated that when there is involvement of the mucous membranes, it is most common in the vesiculobullous type of eruption, and it usually dominates the clinical picture. Its incidence has been estimated by Keil[2] at from 25 to 60 per cent. Any or all of the mucous membranes may be involved. Oral lesions are bullous from the onset and erosion develops quickly. There is extensive swelling of the lips, gums, and tongue. Lesions of the glans penis may produce adhesions. Dyspnea results from edema of the larynx. Involvement of the tracheobronchial mucosa may lead to bronchopneumonia. Duke-Elder[3] has described three types of conjunctivitis that may occur: a catarrhal type that heals in a few weeks; a purulent type that may cause a panophthalmitis resulting in blindness; and a pseudomembranous type with corneal involvement and symblepharon. Usually lesions on the mucous membranes continue to form for several months and heal without scarring. Conjunctival lesions represent an exception where there may be persistence for many years. Mucosal lesions are responsible for the acute emergencies that may arise in this disease.

The course of the disease may be mild with only the skin eruption and pruritus, or severe with prostration and temperature as high as 105° F. The disease may be accompanied by arthralgia, vomiting, albuminuria, and salivation. Constitutional symptoms are absent or mild unless the mucous membranes are involved.

Extensive bacteriological, serological, pathological, and virus studies have failed to identify a causative organism. To further confuse the etiology, there may be a history of contact by way of mouth or externally with drugs or chemicals either in therapeutic or toxic doses. Cases have been reported following the use of sulfadiazine (Dardinski[4]), phenytoin sodium (Ellis[5]), and exposure to sick dogs (Bradlow and Schless[6]). Kove[7] reported a case that developed during convalescence from mumps. Evidence suggesting a possible infection with a psittacosis-like virus was reported by Finland, Jolliffe, and Parker.[8] Weisberg and Rosen[9] suggested avitaminosis B as a causation and reported three patients successfully treated with nicotinic acid.

From the Pediatric Department of Harlem Hospital, Dr. Morris Gleich, Director.

Most cases last from two to five weeks, but there may be recurrences at frequent intervals. There is no evidence that this is a contagious disease. However, Keil[2] states that one case of this sort in the community generally means that more will be seen shortly. Most cases occur in the spring and autumn. There seems to be a predilection for young males. The prognosis depends on the extent and severity of the mucous membrane involvement. Deaths are due to atypical pneumonia and, to a lesser degree, to extensive secondary infection. There is no specific therapy.

During the past year both the severe and the mild types of erythema multiforme exudativum have been seen on the Pediatric Service of Harlem Hospital. The two cases that are being presented showed marked differences in clinical course and response to therapy. They are being reported in support of the arguments of Kove[7] and Murphy[10] who feel that severe cases with mucosal involvement should be classed as a separate entity.

CASE REPORTS

CASE 1.—C. P. was admitted to Harlem Hospital on Sept. 25, 1949, for lethargy, fever, and vomiting of three days' duration, and for what the mother described as "fever blisters" of two days' duration. No history of any previous illness other than measles was obtainable. The patient was delivered normally and had a birth weight of 6 pounds, 5 ounces. He sat up at 7 months of age, and walked and talked at 18 months. The mother and father were both living and well. Of possible significance was that the father was painting the apartment in which they lived on the same day that the patient's illness began.

Physical examination revealed a well-developed, well-nourished, 3-year-old Negro male who was acutely ill and lethargic. The temperature was 103° F. The skin was hot and dry and there were herpetic lesions on the lips. Tearing and a small amount of purulent exudate were present in both eyes. The lids were edematous and the conjunctivae were hyperemic. A mucoid discharge was present in both nostrils. The pharynx was injected, and the tonsils were benign. Several white patches were present over the tongue and mucous membranes of the mouth. Coarse râles and rhonchi were present in both lung fields. The heart rate was rapid; no murmurs were heard and the heart was not enlarged. The abdomen was soft, flat, and nontender.

Within twenty-four hours after admission, an erythematous macular and vesicular eruption appeared and quickly became bullous. The lesions spread rapidly from their origin on the face to involve the neck, torso, and extremities, and the patient developed a urethritis. A diagnosis of Stevens-Johnson's syndrome with bronchopneumonia was established.

On the second hospital day, the patient's condition was critical. Large denuded areas appeared as rapidly as the bullae ruptured. The patient continued lethargic. He had been treated with boric acid irrigations for the eyes and 300,000 units of penicillin each day since admission. Petrolatum gauze dressings were applied to the skin lesions. In addition, the patient received 200 c.c. of whole blood.

Because the skin lesions were worse, penicillin therapy was replaced by aureomycin in a dosage of 50 mg. per kilogram of body weight. By the sixth hospital day, the temperature was 98.6° F., and the skin lesions had begun to dry. The patient was rational for the first time since admission.

Blood and spinal fluid cultures were consistently sterile. Blood chemistries and blood counts were within normal limits. Alpha streptococcus was cultured from the throat; *Staphylococcus aureus* was cultured from the eyes.

No new lesions were noted after the fifth hospital day. Aureomycin was

discontinued on the sixteenth hospital day, and the patient was discharged seven weeks after admission. At that time he had several large areas of hyperpigmentation over the face, and dime-sized hypopigmented areas were present over the neck, torso, and extremities. The nails were hypertrophic and loosened from the base. The general condition was good.

CASE 2.—J. B., a 5½-year-old Negro male, was admitted to this hospital on Jan. 21, 1950, for severe pruritis. He had been in a state of good health until January 12, when his mother noticed a large blister on his right knee. This lesion was aspirated and dressed in the Emergency Unit, and the patient was sent home. Subsequently, bullous lesions appeared on the buttocks, back, and lower extremities. There was no history of any previous illness other than chicken pox three years ago. There was no history of chemotherapy.

Physical examination revealed a well-developed, alert, cooperative patient complaining of itching. The temperature was 100° F., the pulse was 88, and the respirations were 18. Numerous bullae varying in size from 1 to 3 cm. were present over the occipital region of the head, buttocks, knees, and elbows. Several bullae had coalesced and a few had ruptured, leaving large denuded areas. In other places the lesions had crusted. No lesions were present on the mucous membranes, but there were two small vesicles on the vermilion border of the lower lip. The lungs were clear to auscultation and percussion. There was a soft systolic murmur at the apex; there was no cardiac enlargement. The abdomen was soft, flat, and nontender. The axillary, cervical, and inguinal lymph nodes were palpable. The admitting diagnosis was bullous eruption of unknown origin. On the second hospital day, the dermatologist made a diagnosis of erythema multiforme bullosum.

Laboratory work-up revealed a normal urine, total blood protein 5.03, albumin 3.02, globulin 1.97, hemoglobin 75 per cent, white blood count 12,000, and red blood count 3,200,000. *Bacterium coli* and gamma streptococcus were cultured from the skin lesions.

The patient was treated with 50 mg. of aureomycin per kilogram of body weight per day and 50 mg. of Pyribenzamine every six hours. A heat cradle was placed over the lower extremities. New bullae continued to form over the torso and the extremities. They enlarged rapidly, coalesced, became hemorrhagic, and then ruptured. On the ninth hospital day, the lesions began to dry. However, on the eighteenth hospital day, after nine days of seemingly clinical improvement, the temperature spiked to 103° F. and a new crop of bullae appeared on the face, buttocks, and around the genitalia. Aureomycin therapy was replaced by penicillin and 5 per cent sulfathiazole ointment locally. By the next day, the lesions were again drying and the temperature was 99° F. Subsequently, the patient's general condition seemed good in spite of continued low-grade fever until one month later when the temperature again rose to 104° F. At that time the patient complained of severe generalized pruritis, and another crop of bullae appeared on his face.

This patient remained in the hospital for six months, and continued to develop vesicles and bullae at intervals of about two weeks. At no time were all the lesions in the crusted stage prior to his discharge.

DISCUSSION

Until recently, erythema multiforme exudativum was seldom seen in hospitals or private practice. This may be attributed to the multiplicity of names by which the disease is known. Credit is given to von Hebra[11] for the original description of this condition. Bazin[12] denied the unity of the disease and was the first to recognize lesions in the mouth and prodromal constitutional symptoms in the vesiculobullous

type. Since his time, the severe pluriorificialis type has been reported under names other than erythema multiforme exudativum, suggestive evidence of the feeling that this is a separate disease.

In 1922, Stevens and Johnson,[13] thinking that they were describing a new disease, reported two cases of eruptive fever with stomatitis and ophthalmia. This syndrome now bears their name. In 1937, Klauder[14] reported thirty-seven cases of ectodermosis erosiva pluriorificialis. Cases of Stanyon and Warner[15] were reported under the title of mucosal respiratory syndrome. Fletcher, and Harris,[16] Keil,[2] and Lever[1] are among those who have stressed the essential identity of these cases with erythema multiforme exudativum. Costello and Vandow[17] have suggested the name erythema bullosum malignans-pluriorificialis to describe the severe type.

Several factors favoring the classification of cases with severe mucosal involvement apart from erythema exudativum multiforme are suggested by the clinical courses of the reported cases. The first patient became ill suddenly. He was acutely ill and lethargic with bronchopneumonia on admission. His skin lesions changed rapidly from one stage to another eventually becoming bullous. The mucous membranes were involved early. Adequate dosages of penicillin did not affect the bronchopneumonia, but there was a prompt response to aureomycin. No new lesions appeared after the fifth hospital day. This patient made a quick and uneventful recovery without sequellae.

The second patient was never ill enough to warrant confinement to bed except for fear of secondary infection and when a new crop of lesions appeared. The lesions were vesiculobullous from the onset. His hospitalization extends over a long period. At no time was he entirely free of lesions. There were no constitutional symptoms, and no involvement of the mucous membranes. Adequate courses of penicillin and aureomycin failed to institute a cure.

SUMMARY

Two cases of erythema multiforme exudativum with distinct clinical differences have been presented. One, representing the severe pluriorificialis type, made a dramatic response to therapy. The other, a mild case with only a skin eruption, responded to no therapy, and the patient remained hospitalized over a long period for frequent recurrences of vesiculobullous skin lesions.

Although the causative agents in these two variants of the disease are not known, we feel that they are separate entities. However, the many names now in use for describing all of the variants have confused the recognition and reporting of cases. It is suggested that cases be reported under one name until a sound classification is made.

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ERYTHEMA MULTIFORME AS A MANIFESTATION OF NEONATAL SEPTICEMIA

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SEPTICEMIA in the newborn infant is a serious disease. Before the advent of chemotherapy and antibiotics, the outcome of such an infection was almost universally fatal.[1] The availability today of specific treatment for many of the organisms causing this condition makes it imperative that the diagnosis be established at the earliest possible moment. The paucity of associated signs and symptoms and the absence of characteristic manifestations in some cases makes the clinical diagnosis of septicemia in the newborn infant a difficult one. Recently, seven newborn infants with septicemia have been observed. Erythema multiforme was one of the early physical findings shown by three of these patients.

It is the purpose of this paper to emphasize that the appearance of erythema multiforme in a newborn infant should be regarded as an indication of possible septicemia. The literature on this subject has been reviewed.

REVIEW OF THE LITERATURE

A complete, but not exhaustive, review of the English literature failed to reveal any mention of erythema multiforme in association with 111 reported cases of septicemia in the newborn infant.[1-11] Dunham cited three foreign reports of cutaneous lesions associated with neonatal sepsis.[1] In one instance, the eruption was described as morbilliform in nature. In her own series of thirty-nine cases of septicemia in the newborn infant, she described the skin manifestations as localized cutaneous infections consisting of erysipelas, pemphigus, and localized abscesses. She made no mention of lesions resembling erythema multiforme, although the skin manifestations in one instance (Case 14) are described as "erysipelas-like." More recent reports in the literature of fifteen and twenty-five cases of sepsis in the newborn infant discuss the physical findings in detail without mention of erythema multiforme.[9, 10]

CASE REPORTS

CASE 1.—S. B. This was the first admission of a 16-day-old white female infant with a rash of one day's duration. She was born at full term by a normal delivery and weighed 8 pounds, 4 ounces. The patient was breast fed, and developed normally until the day of admission when she was noted to have a generalized rash. There was no history of vomiting, diarrhea, anorexia, or lethargy.

Physical examination on admission revealed a well-developed, well-nourished, active, alert, nonicteric, well-hydrated, white female infant who did not appear ill. Rectal temperature was 101.8° F. Over the body were numerous oval or round, flat, coalescent, erythematous lesions varying in size from a few millimeters to 1 or 2 cm. in diameter and blanching on pressure. The liver was palpable one fingerbreath below the right costal margin. The umbilicus was red and inflamed but without discharge. The remainder of the examination was normal.

From the T. C. Thompson Children's Hospital.

Laboratory data showed a white blood cell count of 27,300 per cubic millimeter, of which 84 per cent were polymorphonuclears. The red blood cell count was 4.80 million per cubic millimeter. A blood culture drawn on admission grew a pure culture of beta hemolytic streptococci.

Course.—The patient was started on aqueous penicillin 30,000 units intramuscularly every three hours and given an evaporated milk formula. Within twenty-four hours, her temperature fell to normal. On the second hospital day, the rash started to fade, beginning with central clearing of the lesions which produced typical erythema circinata. At no time were petechiae seen. Her hospital course was uneventful, and she was discharged on the sixth hospital day after having received five days of penicillin therapy. A follow-up examination one month later revealed a normal infant.

CASE 2.—G. C. This was the first admission of a 12-day-old white male infant who was the product of a full-term, normal delivery. Birth weight was 8 pounds, 7 ounces. The patient was breast fed, and did well until the age of 10 days when he began to nurse poorly and developed a low-grade fever. There was no vomiting, diarrhea, or lethargy.

Physical examination on admission revealed an irritable, active, nonicteric, well-developed, fairly well-hydrated white male infant who appeared only slightly ill. Rectal temperature was 101.4° F. Over the face and arms were several erythematous areas. No petechiae were seen. The umbilicus appeared normal, and there was a moderate amount of crusting at the site of a circumcision. The remainder of the physical examination was normal.

Laboratory studies revealed a white blood cell count of 26,800 per cubic millimeter with 96 per cent polymorphonuclears; red blood cell count of 4.67 million per cubic millimeter; and a normal urinalysis. Unfortunately, a blood culture was not obtained.

Course.—The patient was started on penicillin 30,000 units intramuscularly q. 3 h. and aureomycin 50 mg. by mouth q. 8 h. Parenteral fluids were needed because of initial refusal of feedings. After a temperature spike to 104.4° F. by rectum, the patient ran a low-grade fever for ten days. Within twelve hours after admission the rash on the arms and face spread over the body and consisted of numerous erythematous maculopapular lesions of various sizes. These cleared gradually over a ten-day period. On the third hospital day a fluctuant subcutaneous mass appeared just lateral and inferior to the left sternoclavicular junction. Two days later a similar swelling presented posteriorly in the left upper chest. It was felt that these masses represented metastatic soft tissue abscesses, and they were incised to prevent possible retrograde dissection into the mediastinum. Smear of the pus obtained showed many gram-positive streptococci, but a culture failed to produce growth. An x-ray of the chest at this time showed no abnormality of the lungs, soft tissues, mediastinum, or bones. Concomitant with the appearance of the above masses, a transient swelling was noted in the region of the lower one-third of the left humerus.

The patient's condition gradually improved. Repeat x-ray of the chest on the twelfth hospital day showed osteomyelitis of the left clavicle. It was then apparent that probably the incised masses represented extension of an osteomyelitis of the clavicle. He continued to do well and remained afebrile. On the fourteenth hospital day a white blood count was 10,500 per cubic millimeter with 40 per cent polymorphonuclears.

He was discharged on the eighteenth hospital day, weighing 7 pounds, 15 ounces. Penicillin was continued at home in the form of fortified procaine penicillin, 200,000 units intramuscularly daily, for a total of thirty days of penicillin therapy. An x-ray of the clavicular region at this time showed no evidence of active infection.

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At a follow-up examination one month later the patient was apparently well.

CASE 3.—F. G. (Fig. 1). This was the first Children's Hospital admission of a 16-day-old white male infant with the complaint of swelling of the testicles of twenty-four hours' duration. The patient was a full-term normal delivery, weighing 9 pounds, 5½ ounces. Except for a palpable spleen tip, the infant appeared normal at birth, and he was discharged from the hospital at the age of 8 days. At 2 weeks of age he became anoretic, and the following day bilateral enlargement of the testicles was noted. The family physician was called who found a bilateral orchitis, and temperature of 102° F. rectally. Penicillin in oil, 300,000 units, was given intramuscularly. The next day the patient developed a generalized erythematous rash, and he was admitted to the hospital. There had been no vomiting, diarrhea, or lethargy.

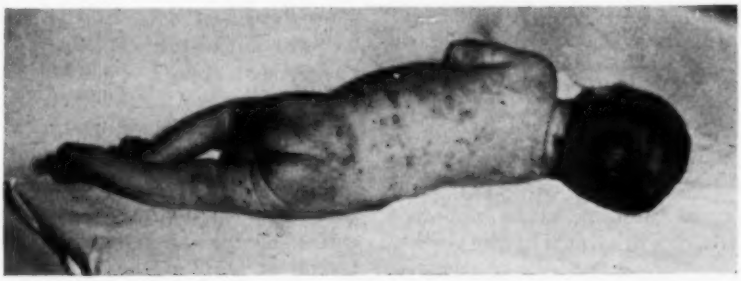

Fig. 1.—F. G. appearance of skin lesions on the day after the rash appeared.

Physical examination showed a moderately ill white male infant in no acute distress with a rectal temperature of 99° F. There were areas of erythema of various sizes over the face, trunk, and extremities (Fig. 1). No petechiae were seen. The umbilicus was red and irritated with a slight amount of mucopurulent secretion. The scrotum was red, hot, and tender with bilateral testicular enlargement. The larger testicle measured 2.9 cm. in width and 3.4 cm. in length. The remainder of the examination was within normal limits.

Laboratory studies revealed a white blood cell count of 15,000 per cubic millimeter with 84 per cent polymorphonuclears. The red blood count was 4.30 million per cubic millimeter. Urinalysis was normal. A blood culture grew a profuse number of hemolytic staphylococcal albus colonies in pure culture. The organism was coagulase-negative. A culture from the umbilicus grew predominately hemolytic *Staphylococcus albus* and a few colonies of beta hemolytic streptococci.

The patient was started on penicillin, 30,000 units intramuscularly q. 3 h., and aureomycin 25 mg. by mouth q. 4 h. The penicillin was increased to 100,000 units intramuscularly q. 3 h. the following day when the blood culture was reported. After some initial anorexia, the patient began to take feedings well. He remained afebrile and clinically showed improvement forty-eight hours after admission. His rash began to show central clearing and gradually faded over a five-day period. The testicles and scrotum slowly decreased in size. Aureomycin was discontinued on the sixth hospital day and penicillin was stopped on the thirteenth hospital day. The patient was discharged on the fifteenth hospital day, weighing 8 pounds, 12 ounces. At a follow-up examination two weeks later the patient was asymptomatic and weighed 9

pounds, 13½ ounces. Both testicles appeared normal in size but the epididymis of the right testicle was thought to be slightly enlarged.

DISCUSSION

Erythema multiforme is a syndrome consisting of the skin manifestation of morbidity elsewhere in the body.[12] It probably represents an allergic response which may be elicited by a variety of allergens. Infection, drugs, foods, rheumatic fever, and tuberculosis have been specifically mentioned in the literature as etiological agents.[12, 13, 14] In our patients it would seem that the rash was a nonpurpuric cutaneous manifestation of blood stream invasion.

The first patient at the age of 16 days developed erythema multiforme and fever as the only manifestations of septicemia. Although she appeared only slightly ill, a blood culture grew beta hemolytic streptococcus. The response to intramuscular penicillin was dramatic. The umbilicus was the likely initial focus for the infection.

The symptoms of the second patient began at 10 days of age and consisted of low-grade fever, anorexia, and irritability for forty-eight hours prior to hospitalization. Then a generalized erythematous multiform rash appeared. His course was complicated by the development of a possible abortive osteomyelitis of the left humerus and a suppurative osteomyelitis of the left clavicle. The patient was treated with penicillin for thirty days and aureomycin for ten days. The presence of these multiple foci of infection with the recovery of streptococci from a fluctuant mass on the left shoulder makes the diagnosis of streptococcal septicemia a likely one even though a blood culture was not obtained. A possible portal of entry was the circumcision.

The third patient developed anorexia, fever, and orchitis at 16 days of age. Thirty-six hours later, an erythematous rash appeared. As the patient received an injection of penicillin in oil prior to the appearance of the rash, the possibility cannot be excluded that the skin lesions resulted from allergy to penicillin or the oil. A blood culture grew hemolytic *Staph. albus* which was not thought to be a contaminent although the organism was coagulase-negative as the patient had previously received penicillin. After contact with antibiotics, pathogenic staphylococci may appear on culture as variants which have lost their pathogenicity, do not produce exotoxin, and have changed morphological and cultural characteristics.[18] A similar organism was obtained from the umbilicus. The patient responded well to treatment with oral aureomycin and parenteral penicillin. The umbilicus was thought to be the site of invasion of the organism. Orchitis complicating septicemia in the newborn infant has previously been reported.[1]

In these three patients the rash began between the ages of 10 and 16 days as small erythematous splotches on the face which quickly spread over the body and extremities in varying sizes and often becoming confluent in nature. After twenty-four to forty-eight hours, the lesions in all cases showed central clearing, leaving circinate areas which gradually faded over a period of three to seven days. No stomatitis, vesicles, petechiae, or pustules were noted.

The erythema multiforme shown by these patients was most likely a dermatological response to septicemia.

However, the conclusion that all such rashes in the newborn infant are an indication of blood stream infection is certainly not warranted. The occurrence of an erythematous rash during the early neonatal period is common and has been called "toxic erythema" or "flea bite dermatitis."[15, 16, 17] This usually consists of slightly raised macules surrounded by a ring of erythema and at times may resemble a wheal. It is a benign condition of obscure etiology which may appear from a few hours to several days following birth. The frequent appearance of "toxic erythema" in the newborn infant may cause the physician to minimize the significance of an erythematous rash in this age group. However, the experience gained from our patients would indicate that an erythematous rash in the newborn infant should not be lightly dismissed, especially if it appears after the first week of life. Patients with such a rash should be examined carefully from a clinical and laboratory standpoint in order to ascertain whether or not there is an associated infection.

SUMMARY

1. Three cases of erythema multiforme associated with septicemia in newborn infants are presented.

2. The literature on this subject has been reviewed.

3. The presence of an erythematous rash in the newborn infant should not be lightly dismissed and should be regarded as a possible indication of septicemia.

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ILEOCECAL INTUSSUSCEPTION CAUSED BY LYMPHOID HYPERPLASIA

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THE etiology of intussusception in infants has never been satisfactorily understood. Perrin and Lindsay[1] in their monograph on intussusception in 1921 state, "A (direct) relation is seen to exist between the quantity of lymphoid tissue in the last few inches of ileum and the age incidence of ileocolic intussusceptions." They believed that the majority of intussusceptions are caused by inflammatory swellings of lymphoid tissue. They showed that the age incidence of lymphoid overgrowth in the terminal ileum paralleled the age incidence of intussusceptions, 1 year of age or younger.

This explanation has not received much acceptance. Oberhelman and Condon[2] specifically state that there was no mention of intestinal lymphoid hyperplasia in their series of ninety-five cases. Other series also classify as "due to unknown cause" the great majority of intussusception in childhood. Hogg and Donovan[3] have 83 per cent of their series without an etiological explanation, but give as the cause in 11 per cent enlarged mesenteric lymph nodes at the ileocecal area. Smith[4] gives lymphoid hyperplasia as cause in three cases out of a series of thirty-five. Ladd and Gross[5] do not mention lymphoid hyperplasia although they report one case caused by a lymphoma.

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Dennis[6] in reporting a series of intussusceptions treated by resection and primary anastomosis includes two cases (one by way of a footnote) caused by lymphoid overgrowth. It is interesting to note that each of these recurred after initial reduction; in one the reduction was operative but the intussusception recurred in five days necessitating reoperation and resection; in the other, primary reduction had been accomplished by barium enema but recurrence twenty-seven hours later required operation and resection.

The following case reports show two instances, in each of which the intussusception was very obviously caused by enlargement of normally placed lymphatic tissue. In one it was a Peyer's patch, in the other a circular cuff of lymphatic tissue.

CASE REPORT

CASE 1.—C. C. (New York Hospital No. 533 550), an 11-month-old female infant, was brought to the hospital on Feb. 19, 1949, because of rectal bleeding. The child had been in good health until two days before admission when she had a temperature of 104° F. There was no apparent explanation for this and the temperature gradually fell toward normal. The morning of the day of admission she gave evidence of intermittent abdominal pain, began to vomit, and passed several bloody stools.

On physical examinations the child was well nourished but lethargic. Temperature was 38.3° C., pulse 120 per minute, respiration 20 per minute.

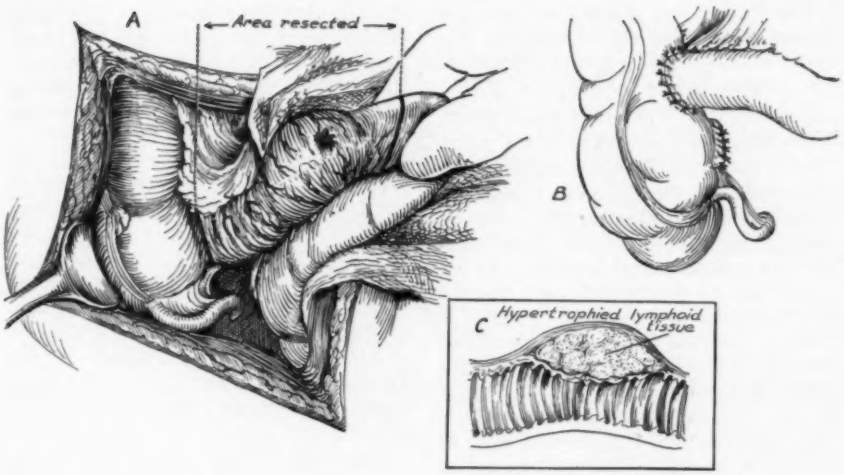

Fig. 1 (Case 1).—*A*, Sketch of region of ileocecal valve following reduction of intussusception. Hypertrophied Peyer's patch presents as a definite mass in the distal ileum. *B*, After resection of ileum and ileocecostomy. *C*, Section of ileum showing intraluminal projection of the Peyer's patch.

Fig. 2 (Case 1).—Low-power magnification of section of ileum showing hemorrhagic Peyer's patch.

There was an indefinite sausage-shaped mass lying transversely in the upper abdomen and currant jelly stool was present in the rectum.

Laboratory.—Urinalysis was normal, hemoglobin 11.5 Gm., red blood count 5.0 million, white blood count 13,100.

Operation.—The patient was hydrated and then taken to the operating room. Laparotomy was performed through a right rectus incision. An intussusception was found with the intussusceptum just beyond the splenic flexure. Reduction was accomplished without difficulty. Inspection of the distal ileum disclosed a mass 3 × 2 cm. in size. This mass gave a discoid, puckered appearance to the ileum and, at first, the operator thought it represented a foreign body in the ileum. However, it could not be dislodged or milked either proximally or distally and therefore was deemed an intrinsic lesion of the bowel. In order to determine the nature of this mass, a small opening was made in the ileum adjacent to the mass. The lesion was a hemorrhagic, swollen Peyer's patch. Inasmuch as this engorged patch formed such a definite mass and obviously was the lead for the intussusception, it was thought that recurrence was inevitable if it were left in situ. Accordingly, 5 cm. of the ileum were resected and an end-to-side ileocecostomy performed (Fig. 1). Her postoperative course was smooth, and barium enema on her twelfth postoperative day demonstrated a patent stoma. She was discharged and has remained well.

Pathology.—The gross lesion was a sharply demarcated hemorrhagic Peyer's patch. Microscopic studies showed hyperabundance of lymphoid follicles (Fig. 2).

CASE 2.—S. S. (New York Hospital No. 547 643), a 4½-year-old boy, was admitted to the New York Hospital on Aug. 8, 1949, because of abdominal pain. Two days before admission the youngster had diffuse abdominal pain that subsided after one day only to recur the day of admission. The pain did not seem cramplike, was not localized, and was not associated with vomiting. For the four days preceding admission the child had had a cough and other evidence of an upper respiratory infection. On physical examination he was a well-nourished child obviously in pain. Temperature was 39° C., pulse 88 per minute, respiration 20 per minute. There was marked tenderness in the right lower quadrant of the abdomen with a suggestion of rebound tenderness.

Laboratory.—Urine showed 1 plus acetone, hemoglobin 14 Gm., red blood count 5.2 million, white blood count 10,500.

Operation.—The patient was operated on the day of admission, the peritoneal cavity being entered through a McBurney incision. At operation an intussusception was found, 4 cm. of terminal ileum being intussuscepted into the cecum. Reduction was accomplished easily, and it was found that the intussusception was due to a tumor mass apparently involving the entire wall of the ileum in its lower 3 cm. It was felt to be totally unwise to leave this portion of the ileum in place so it was resected and an end-to-side ileocecostomy performed (Fig. 3). The patient was discharged well on his sixteenth postoperative day.

Pathology, Gross.—Beneath the mucosa in the distal part of the specimen are numerous small firm white nodules which measure approximately 2 mm. in diameter. The entire bowel wall is thickened and its cut surface is white in color and there is no apparent invasion of the muscular layers by the overlying submucosal nodules.

Microscopic.—The specimen is covered by normal glandular mucosa. However, within the submucosa are many hyperplastic lymphoid follicles which in many areas have grown to such an extent that the overlying mucosa is thinned out and is represented by a single layer of cuboidal epithelium (Fig. 4).

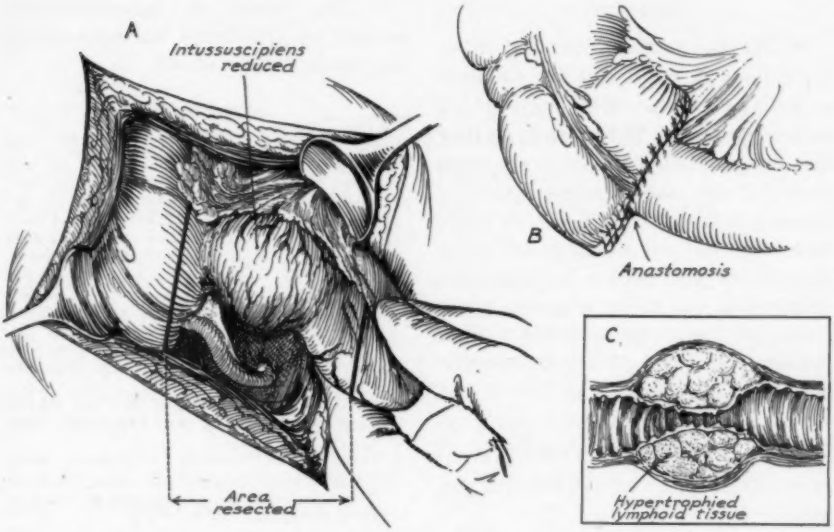

Fig. 3 (Case 2).—*A*, Sketch of region of ileocecal valve following reduction of intussusception. The circular cuff of hypertrophied lymphatic tissue presents as a definite tumorlike mass. *B*, After resection and ileocecostomy. *C*, Section of distal ileum showing localized, lymphatic hypertrophy and its encroachment on the lumen of the bowel.

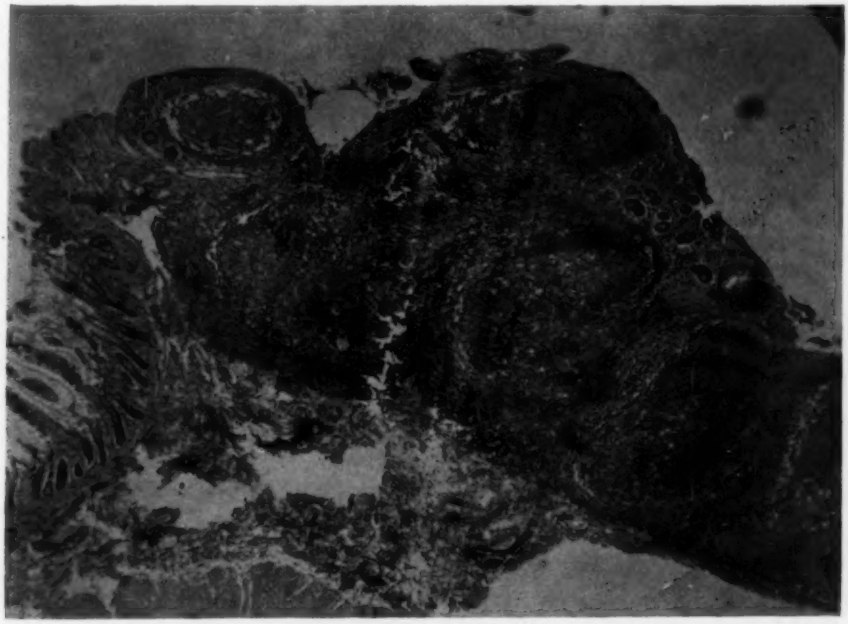

Fig. 4 (Case 2).—Low-power magnification of section of ileum. Normal mucosa is seen on the left. On the right, hypertrophied lymphatic tissue has distorted the mucosa.

DISCUSSION

By far the great majority of intussusceptions in childhood are classified as having an unknown etiology. It has been suggested by Perrin and Lindsay[1] that lymphoid hyperplasia in the ileum accounts for these intussusceptions. There is meant in this paper no direct inference that all unexplained intussusceptions are caused by lymphatic overgrowth, but in the two cases herein presented this overgrowth was unquestionably the cause of the intussusception.

SUMMARY

1. A brief discussion of the etiology of intussusception in childhood is presented.

2. Two cases of intussusception caused by lymphatic enlargement in the ileum are presented.

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PRECOCIOUS SEXUAL DEVELOPMENT

A Study of Thirty Cases

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IN THE past eleven years we have had the opportunity to study in detail thirty patients who have manifested precocious sexual development. All of these patients have been followed for a period of at least one year and many of them for a longer period of time. All were children under 13 years of age when first seen at the University Hospital, and they represent a fairly average cross section of patients who present themselves to the pediatrician with similar developmental abnormalities.

The purpose of presenting this material is to give an analysis of the causes of abnormally early sexual development in such a group, to outline the presently available methods of diagnosis, and to report the eventual outcome of several of the patients as they approach adult life. Although many individual case presentations of a similar nature have been made and some series have been reported with a common etiological basis, we are aware of only one recent study dealing with a relatively unselected group of patients with a common chief complaint of precocious development. This is a collected series of fifty-four patients by Wilkins[47] (excluding his cases of "intersexuality").

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No absolute criteria have been established for the average time of development of primary and secondary sexual characteristics. We have used the following signs or symptoms as indicating abnormally early sexual development. These are based upon our own observations as well as those of Stuart,[39] Talbot,[40] and Reynolds and Wines.[34]

1. Breast enlargement before 8 years of age.
2. Menarche before 10 years of age.
3. Pubic or axillary hair developed before 9 years, especially if dark and coarse.
4. Enlargement of clitoris or penis disproportionate with age of subject.
5. Other associated phenomena at disproportionate ages: facial hair, acne, change in voice, pigmented areola, and pigmentation of the sexual organs.

Table I shows the distribution of the patients arranged in chronological order according to age of onset of the first symptom. The criteria used in the table for stature were the Iowa growth charts of Jackson and Kelly.[24] Any child falling above the 67 per centile line on those charts was considered advanced in statural growth. The standards established by Todd[43] and others for skeletal maturation were used in estimating the degree of bone development. Skeletal maturation was considered advanced (+) if it was at least two years beyond that expected

TABLE

CASE NO. INITIALS SEX	AGE ONSET SYMPTOMS	HISTORY AND PHYSICAL EXAMINATION	STATURE	BONE MATURATION
1. G. L. Female	Birth	Enlarged clitoris, pubic hair at 2 years, question of true sex.	A	++
2. L. M. Male	Birth	Pubic hair and enlarged penis at 1 year.	A	++
3. D. C. Female	Birth	Enlarged clitoris and pubic hair at 2 years.	A	++
4. D. B. Male	Birth	Enlarged penis, pubic hair and acne at 9 months, deep voice. Abnormal pyelogram at 4 years.	N	++
5. B. B. Female	Birth	Large clitoris, pubic hair at 5 years, question of true sex. No vaginal opening.	A	++
6. C. J. Female	Birth	Large clitoris, pubic and axillary hair at 6 years.	A	++
7. R. L. Female	Birth	Large clitoris, pubic and axillary hair at 4 years, vaginal bleeding at 5 years and enlarged breasts. Mental retardation and macrocephaly since birth.	A	++
8. J. B. Female	Birth	Large clitoris, pubic hair at 10 months.	A	+
9. R. V.	Birth	Large clitoris, pubic hair at 11 months. No vaginal orifice. Question of true sex.	A	++
10. H. M. Female	4 mo.	Breast enlargement, pubic hair. Left facial paralysis and mild convulsions since birth.	N	N
11. M. S. Female	1 yr.	Pubic hair and enlarged clitoris. Pyelogram revealed suprarenal mass.	N	N
12. E. C. Male	1 yr.	Obesity (89 pounds at 2 years), hirsutism, acne, hypertension, deep voice, diabetic glucose curve.	A	++
13. P. S. Female	14 mo.	Sudden breast enlargement. No other findings.	N	N
14. V. P. Female	18 mo.	Breast enlargement and pubic hair. Convulsive seizures.	A	++
15. R. I. Female	2 yr.	Breast enlargement, vaginal bleeding, "growth" over left eye, areas of skin pigmentation. Cystic areas in bone by x-ray.	A	+
16. J. P. Female	2 yr.	Vaginal bleeding at 2 and 5 years, breast hypertrophy and pubic hair at 3½ years.	N	+
17. C. B. Female	2 yr.	Sudden breast enlargement. No other findings.	N	?
18. R. M. Female	2½ yr.	Breast enlargement, slight pubic and axillary hair development, milky vaginal discharge. Mumps 4 weeks before onset of symptoms.	N	N
19. J. K. Female	5 yr.	Breast hypertrophy followed by pubic and axillary hair. Menarche at 9 years.	A	?
20. D. W. Female	5 yr.	Breast hypertrophy, pubic and axillary hair. Several fractures. Pigmentation of skin and bone cysts by x-ray. Menarche at 9 years.	A	+
21. N. V. Female	6 yr.	Breast enlargement and pubic hair.	A	+
22. C. M. Female	6 yr.	Breast enlargement, pubic and axillary hair. Menarche at 7 years.	A	+
23. N. H. Female	6 yr.	Breast enlargement, pubic and axillary hair. Severe mental retardation since birth.	A	N

(Table continued

BONE MATURATION	HORMONE STUDIES	DIAGNOSIS	THERAPY	COMMENT ON PROGRESS
++	17-K 36.6 Est. 10 R.U.	Pseudohermaphrodite, adrenal cortex hyperplasia	Laparotomy clitorotomy	Living and well at 6 yr. Still very masculine, timid.
++		Adrenogenital syndrome probable hyperplasia	None	Living and well at 6 yr. Large for age.
++		Adrenogenital syndrome hyperplasia of cortex	Laparotomy clitorotomy	Little change at 4 yr.
++	17-K 6.8	Carcinoma of left adrenal cortex	Surgery—excised tumor	Postoperative death due to atelectasis.
++	17-K 18.5 Est. 4 R.U. F.S.H. 0	Pseudohermaphrodite, adrenal cortex hyperplasia	Laparotomy	Timid, treated as a girl, poor work in school at 8 yr.
++	17-K 45	Pseudohermaphrodite, adrenal cortex hyperplasia	Laparotomy, clitorotomy	At 9 yr. does well in school and socially, still masculine in appearance.
++	17-K 10.3 F.S.H. +++	Hydrocephalus, etiology unknown	Pneumoencephalography	No essential change at 7 yr.
+	17-K 10.8 Est. 8 R.U. F.S.H. 0	Adrenogenital syndrome hyperplasia of cortex	Laparotomy, clitorotomy, estrogen	Menses induced with estrogen at 13 yr. with breast hypertrophy. Hirsutism and virilism unchanged otherwise.
++	17-K 14	Pseudohermaphrodite, adrenal cortex hyperplasia	Laparotomy, clitorotomy at 4 yr.	Death at 7 yr. due to air embolism following perirenal insufflation.
N	17-K 2.4 Est. 3 R.U. F.S.H. + Vag. ep. ++	Porencephaly	Pneumoencephalogram	No changes for 3 yr. when lost for observation.
N	17-K 78 Est. 0 F.S.H. 0	Carcinoma of left adrenal cortex	Surgery—excised tumor	Operation at 2 yr., doing well at 6½ yr. All signs and symptoms regressed.
++	17-K 4.5 F.S.H. +	Cushing's syndrome	None	Progression of all signs during 18 mo. patient was followed.
N	17-K 2.0	Simple breast hypertrophy	None	Breasts became normal in 8 mo. Normal girl at 6 yr.
++	17-K 4.0 Est. 2 R.U. F.S.H. ++	Tumor of third ventricle	Sedatives for convulsions	Alive at 9½ yr., physically mature, obese, a serious behavior problem, rare convulsions, no menses.
+	17-K 2.0 Est. 6 R.U.	Polyostotic fibrous dysplasia	None	Well at 10 yr. with physical development of mature woman. Menses still irregular. Does average school work.
+	17-K 1.8 Est. 2 R.U. Vag. ep. ++	Precocious puberty	None	Well at 11 yr., no problems socially or psychologically. Regular menses at 9 yr.
?	17-K 0.5 Est. 0	Simple breast hypertrophy	None	Well at 7 yr. Breasts practically normal in 18 mo.
N	17-K 2.32 Est. 4 R.U. F.S.H. 0	Unclassified	None	Regression of all abnormal findings over a year's period. Normal at 5 yr.
?	17-K 2.4	Precocious puberty	None	At 12 yr. is a completely normal but well-matured girl, menses regular.
+	Est. 10 R.U.	Polyostotic fibrous dysplasia	None	"Nervous" but otherwise normal child at 11 yr. School work average, social adjustment good. Regular menses.
+	17-K 2.5 Est. 6 R.U. F.S.H. ++	Precocious puberty	None	Well in every respect at 14 yr., short (61 in.), does well in school. Menarche 10 yr.
+	17-K 4.6 Est. 8 R.U.	Precocious puberty	None	Well at 9 yr. but appears older than her age. Menses regular for past year.
N	Vag. ep. ++	Congenital brain defect	None	Developed choreiform movements, institutionalized at 9 yr.

(continued on next page.)

TABLE I

CASE NO. INITIALS SEX	AGE ONSET SYMPTOMS	HISTORY AND PHYSICAL EXAMINATION	STATURE	BONE MATURATION
24. P. K. Female	6 yr.	Full physical sexual maturation from 6 to 7 years. Regular menses from 7 years. Premature birth but normal development.	A	+
25. J. S. Female	7 yr.	Breast enlargement and pubic hair. Convulsions since neonatal period.	N	?
26. M. R. Female	7 yr.	Breast enlargement and pubic hair following brain abscess and convulsions. Menarche at 8½ yr.	N	+
27. N. B. Female	7 yr.	Breast enlargement, pubic hair and milky vaginal discharge.	N	+
28. G. W. Female	7 yr.	Breast enlargement, pubic and axillary hair. Mental retardation since birth (I.Q. 70).	N	N
29. J. B. Female	8 yr.	Full physical maturity at this age, questionable time of onset. Regular menses at 9 years. Severe mental retardation since birth. Obesity.	A	+
30. S. W. Female	8 yr.	Breast enlargement and pubic hair, menses began at 9 years.	N	N

Stature was considered advanced (A) if it exceeded the 67 per cent line on the Iowa growth chart.[31] Normal is indicated by (N).

Bone maturation was considered advanced (+) if it exceeded chronologic age by at least two years, very advanced (++) if it exceeded chronologic age by more than four years. For the most part Todd's atlas was used as the criterion.[42] Average limits are indicated by (N).

for chronologic age and very advanced (++) if it was more than four years beyond that expected for the chronologic age of the subject. These measurements were often repeated during the period of observation and are indicated in the table only for that period when there was the greatest disparity between age and the given measurements.

Urine assays for 17-ketosteroids were carried out by colorimetric methods. Follicular stimulating hormone (FSH) assays were done by the biological method by the Department of Obstetrics and Gynecology of the University Hospital. Estrogen determinations were carried out biologically until 1947 and since that time by the colorimetric method.

Table II indicates the separation of the thirty patients into groups according to the pathogenesis of their precocious sexual development. Several interesting and valuable findings become apparent. Of the total number of patients only three were males. These figures of a ratio of one to nine agree in general with other reports in the literature.[4, 18, 27, 32, 36, 40] The reason for the preponderance of girls displaying abnormal early development is not easily explained as the site of abnormal physiology exists in both sexes.

The age of onset, regardless of the etiological factor, covers the entire preadolescent years. It is true that so-called early physiologic puberty (Novak)[32] is more likely to have its onset in middle childhood rather than in infancy; however, one of our children with this syndrome was 2 years of age when she first menstruated (Case 16, Table I).

The most common cause of precocious sexual development in our series of patients was the adrenogenital syndrome. Two of the nine children in this group were males. One of each

CONT'D

HORMONE STUDIES	DIAGNOSIS	THERAPY	COMMENT ON PROGRESS
	Precocious puberty	None	Followed in this clinic from birth to 9 yr. with no other abnormal developments. Well adjusted in school and home.
17-K 6.4 Est. 2 R.U. F.S.H. 0	Mixed convulsive disorder (E.E.G.)	Sedatives for convulsions	At 10 yr. is doing well, physically nearly mature, no menses.
17-K 2.8	Brain abscess and convulsive disorder	Sedatives for convulsions	Somewhat of a behavior problem at home and school. Big for age but otherwise well at 13 yr.
17-K 2.4 Est. 2.4 R.U. Vag. ep. ++	Precocious puberty	None	Regular menses since 8 yr. Does well in school. Physically well at 11 yr.
17-K 5.0 Est. 2 R.U.	Congenital brain defect	None	No change in 18 mo. that patient was followed.
	Congenital brain defect	Thyroid for obesity of no benefit	Doing well in a "special" class in school at 17 yr. No essential changes in physical findings.
17-K 2.0 Est. 5 R.U. F.S.H. ++	Precocious puberty	None	At 14 yr. normal-appearing and normal acting girl. Acne still severe at that age.

Hormone studies were carried out on many occasions for many of the individual cases but only representative samples are given. Ketosteroids are indicated 17-K and expressed as milligrams. Estrogens are indicated Est. and expressed as rat units by biological assay. Follicular stimulating hormone (F.S.H.) is graded from 0 to ++++. The degree of cornification of the vaginal epithelium (Vag. ep.) is graded from 0 to ++++.

TABLE II. THE DISTRIBUTION, ACCORDING TO ETIOLOGY AND SEX, OF THIRTY CASES OF PRECOCIOUS SEXUAL DEVELOPMENT STUDIED OVER AN ELEVEN-YEAR PERIOD

TYPE OF PRECOCIOUS DEVELOPMENT	NUMBER OF CASES	
	FEMALES	MALES
Adrenogenital syndrome	7	2
Central nervous system lesion without tumor	7	0
True precocious puberty (physiologic)	7	0
Simple breast hypertrophy	2	0
Polyostotic fibrous dysplasia	2	0
Tumor of central nervous system	1	0
Cushing's syndrome	0	1
Unclassified	1	0
	27	3

sex had an adenocarcinoma of the adrenal cortex proved at operation. The girl has survived over four years at the time of this report and appears healthy in every respect with remission of masculinizing signs (Case 11, Table I). The boy with adenocarcinoma is reported in some detail under *case reports* (Case 4, Table I).

The group with the next largest number of patients is that with associated central nervous system lesions. The group is of interest because none of the seven subjects in this category had any evidence of intracranial neoplasm. In most of these there was evidence of mental retardation, convulsive seizures or both. In one patient precocious development began after she had recovered from a brain abscess secondary to a mastoiditis. Another patient had an associated hydrocephalus since birth and one had porencephaly. We cannot be certain that these coexistent abnormalities of the central nervous system are a direct cause and effect, but the relatively large number of patients with such lesions combined with precocious sexual development seems to be more than a

fortuitous occurrence. Similar cases have been described by other authors.[7, 18, 36, 40, 42, 46]

Early physiologic puberty was found in seven of the patients studied. These were all girls, usually with onset of symptoms between 6 to 8 years of age. In each case no adequate explanation could be found for the phenomena, but all were characterized by a normal pattern of development except that it took place at an early age. There was moderate advancement of physical growth, height, weight, and ossification, and an increase in excretion of estrogens and 17-ketosteroids to adult levels. Markedly abnormal levels of these hormone products were not found in these patients.

Two patients displayed simple precocious breast hypertrophy with slight pigmentation of the areolae in each case. In both instances the onset was abrupt, painless, and unassociated with other evidence of advanced development. Urine hormone assays were within normal limits for both children at the time of maximal breast enlargement. In both cases there was regression of mammary development over a period of several months and no return of signs or symptoms for a period of at least three years. This condition has been described by Talbot[40] as being "relatively rare" and having a good prognosis. The etiology of the syndrome is unknown.

The two girls with polyostotic fibrous dysplasia were typical of this interesting syndrome first described by Albright and associates.[2, 29] In addition to precocious sexual development, each child was advanced in statural and osseous growth, there were scattered areas of brown pigmentation of the skin, cystic areas in the bones, and increased excretion of estrogens for chronologic age.

TABLE III. MAJOR DIAGNOSTIC FEATURES OF THE CAUSES OF PRECOCIOUS SEXUAL DEVELOPMENT IN CHILDREN

Adrenogenital syndrome	Signs of precociousness often present at birth or in early infancy. May be associated with anomalies of the urogenital tract, e.g., the "hypospadia" of the pseudohermaphrodite. Virilization always present and bone maturation markedly advanced. 17-ketosteroids moderately elevated. I. V. pyelograms should be done to rule out tumor.
Precocious puberty	Onset usually after six years and development normal in sequence. No virilization in girls. Bone maturation moderately advanced. Hormone assays show levels of adolescence or adult.
Lesions of the central nervous system	Onset at any age. Neurological signs often present or a past history of disease of the nervous system. Moderate to marked advancement of bone maturation. Hormone excretion in advance of chronologic age but rarely markedly elevated. Sequence of development is orderly but rapid.
Polyostotic fibrous dysplasia	Very similar to above (C. N. S. lesions) but associated with areas of skin pigmentation and cysts of bone. Found almost exclusively in girls.
Breast hypertrophy	There are no other signs of precocious development. Hormone assays are normal.
Primary tumors of the gonads	Palpable tumor frequently present. Normal sequence of development altered. Menstruation before other signs of puberty except for some breast hypertrophy. Bone maturation much advanced in boys, only slightly in girls. Hormone assays greatly elevated above normal (estrogens or 17-ketosteroids), but gonadotropins are low.

One patient with a tumor in the third ventricle and one with Cushing's syndrome were present in this series. Another child was unclassifiable (Case 18). This girl had had mumps one month before onset of breast hypertrophy and hirsutism. It is of interest to note that all of these signs underwent regression over a year's time and at the last examination by her family pediatrician there were virtually no abnormalities present. What relationship, if any, the mumps had to this sequence of events is very difficult to tell. There was no history suggestive of mumps meningoencephalitis or oophoritis.

SELECTED CASE REPORTS

B.B. (Case 5) was first brought to University Hospital at 6 years of age for the purpose of determining her sex. She had had a large clitoris since birth, had always been big for her age, was very boyish in actions and habits, but was raised as a girl. At 5 years of age she had pubic hair, and at the time that we saw her there was also abundant axillary hair. Her height was 48½ inches, and her osseous development was that of a 10-year-old girl. There was no vaginal orifice present. Her voice was low pitched and she had mild acne. Assay of the urine for 17-ketosteroids showed an adult level and the estrogen level was somewhat higher than might have been expected. Exploratory laparotomy revealed normal ovaries and ducts with a very small uterus. Biopsy of both adrenals showed diffuse adrenal cortical hyperplasia.

This patient was a female pseudohermaphrodite with the adrenogenital syndrome. Hyperfunction of the adrenal glands almost certainly existed in intrauterine life and caused the related urogenital tract anomalies. No treatment was attempted. At 8 years of age she was in the second grade (I.Q. 85) and was very shy and timid but otherwise well. Her parents continue to raise her as a girl.

D.B. (Case 4) was first seen at 3 years of age because of an enlarged penis, pubic hair, acne, and a bass voice. His parents stated that he was born with an enlarged penis and that pubic hair appeared before his first birthday. He was seen in this clinic at fairly frequent intervals over a year's time with steady progression of his virilism. Estimations of 17-ketosteroids were carried out four different times with the highest total being 6.8 mg. per twenty-four hours, the last determination being carried out a few days before operation. At 3 years of age his "bone age" was slightly advanced but at 4 years it had progressed to a 12-year level. Intravenous pyelograms were normal at 3 years. But at 4 years there was definite downward displacement of the left kidney. In addition, at this latter date, there was scattered calcification in the region of the left adrenal as seen by roentgenography. His measurements for height and weight were not advanced for age. At operation, an orange-sized left adrenal cortical carcinoma was removed. In spite of all measures the boy died twelve hours after operation of massive pulmonary atelectasis on the left side. There were no postoperative signs of adrenal insufficiency, however, as whole adrenal cortical extract had been given, and frequent checks of blood pressure obtained as a precautionary measure. Autopsy revealed no evidence of metastases and the remaining adrenal cortex was not atrophic.

The above case is of particular interest from several points of view. The presence of an adrenocortical carcinoma at birth can be strongly suspected although this condition has not previously been reported. In all cases of the adrenogenital syndrome present at birth the lesion has either been a benign adenoma or more commonly a diffuse hyperplasia.[4, 21, 37, 46, 47] It is possible that either of these was initially present in this patient and that

there was subsequent development of carcinoma. The relatively low excretion of 17-ketosteroids is very unusual in view of the clinical course, especially the advanced osseous development, and the pathologic diagnosis. It serves to emphasize the fact that a hormonally active carcinoma cannot always be diagnosed by the level of 17-ketosteroids nor by their fractionation into alpha and beta components, which were normal in this boy. Finally, the poor prognosis in such patients from a surgical standpoint is again brought to our attention as it has been by other authors.[16, 19, 26]

J.P. (Case 16) was a 5-year-old girl when first seen at this clinic with a chief complaint of breast enlargement and vaginal bleeding. She had one four-day episode of vaginal bleeding at 2 years of age and a similar episode at 5 years. Breast hypertrophy was first noted at the time of the first menstrual period and had continued slowly but steadily since then. Pubic hair was present between 3 and 4 years of age. She was at the upper limits of normal for stature when first examined at the University Hospital and her bone age was two years in advance of her chronologic age. Numerous studies were carried out including intravenous pyelography, electroencephalograms, neurological consultations, etc. Vaginal smear showed fairly marked cornification of epithelium. Levels of 17-ketosteroids and estrogens were slightly above those for a child of her chronologic age but below the levels usually found in early adolescence. The patient has been followed since her first visit and has developed in an advanced but otherwise normal manner. Regular menses at twenty-eight to thirty-day intervals began at 9 years of age and have continued. At 10½ years she was doing "good" work in school, was well adjusted psychologically, and appeared slightly larger and considerably older than her chronologic age. Except for the precocious development there were no other apparent abnormalities.

We believe this girl represents a true or physiologic early puberty and is of unusual interest because of the early age at which the first signs and symptoms developed. The long intervals between the first few menses is rather typical in these children. The other patients with this syndrome in our series had very similar histories and physical and laboratory findings. The age of onset, however, was most commonly beyond 6 years of age. The cause of early development in these girls remains obscure. No boys with similar precocious sexual development were encountered during our period of study.

V.P. (Case 14) was seen at 2 years of age with a history of convulsive seizures of six months' duration. Birth and delivery were uneventful and development had been normal until the abrupt onset of the seizures. Physical examination revealed an attractive but extremely irritable little girl who was large for her stated age (height 37 inches, weight 35 pounds). There was marked breast hypertrophy and pigmentation of the areolae. Pubic hair was present. It was coarse, dark, and curly. Osseous development by roentgenographic examination was about four years in advance of her chronologic age. Estimation of 17-ketosteroids and estrogens in the urine were at prepubertal levels. The same relative values were found for follicular stimulating hormone (FSH) in the urine. A pneumoencephalogram revealed a large (walnut-sized) tumor in the floor of the third ventricle without obstructive phenomena being apparent. The parents refused to consider surgery, and she was sent home with sedatives to aid in control of the convulsions. At 9½ years of age, seven years after the diagnosis of a brain tumor was established, this girl was still alive. At that time (November, 1949) she was a considerable behavior problem to her parents and had not attended school because of this. She weighed 180 pounds and was 61 inches tall. Secondary sexual characteristics were completely developed. She con-

tinued to have rare convulsive seizures. She had never menstruated.

This case is fairly typical of those with a brain tumor producing precocious development. Of particular interest is the length of time the patient has lived after the diagnosis was made. Bronstein and associates,[7] however, have stated that long life is not incompatable with hypothalamic tumors. The behavior and obesity that this patient developed are also characteristic of hypothalamic lesions.[3, 42, 44] The pathogenesis in these patients is believed to be either stimulation of the pituitary or nerve tracts leading to the pituitary by the tumor, or the blocking out of inhibiting centers acting upon the pituitary.[42] As a result, true precocious puberty takes place, i.e., all of the factors necessary for both morphologic and physiologic sexual development occur. Menstruation could therefore be expected, and in the majority of such cases it does occur.[3, 44]

M.R. (Case 26). This girl had been followed in our clinic at intervals since 4 years of age. At the time of her initial visit, except for an acute otitis media, she appeared normal. At 5 years of age she developed a mastoiditis, lateral sinus thrombosis, and a brain abscess which were treated successfully at this hospital. Following this, however, there was a marked personality change and several severe convulsive seizures. The latter were easily brought under control with sedatives. At 7 years of age there was rapid development of the breasts, and pubic hair appeared shortly thereafter. She became moderately obese. Irregular menses occurred from 8½ years until at 10 years of age they became regular. Subsequently she has lost weight on a dietary regimen and has been less of a behavior problem. At 8 years she had the osseous development of a 10-year-old girl, and her height was likewise advanced about two years in excess of her chronologic age. Her I.Q. at 8½ years was 95.

The sudden personality changes and precocious development following the severe insult to the central nervous system appear to be more than mere coincidence in this girl. Fortunately, we had seen her before the onset of any of these symptoms and therefore feel more certain of the association. Similar lesions of the central nervous system with precocious development have been described, and the type of lesions have been quite varied.[7, 40, 42] The pathogenesis, in all probability, does not differ greatly from that just pointed out for the preceding patient with the brain tumor. In the above patient we are of the opinion that her prognosis is quite favorable.

Of the seven patients in this group, i.e., with associated central nervous system disorders, four had repeated convulsive seizures, three had marked mental retardation, and one each had hydrocephalus, porencephaly, choreiform movements of all extremities, and the above-described patient a purulent infection of the brain. As mentioned previously, a direct cause and effect in most of these cases is presumed but cannot be proved.

The patient with Cushing's syndrome (Case 12) presented a picture similar to that of other cases described in the literature associated with the findings of the adrenogenital syndrome.[1, 8, 28, 31, 37] He was markedly obese, had hypertension and a typical diabetic glucose tolerance curve but no glycosuria. The cause of the syndrome was not disclosed during the eighteen months that the patient was observed here. Exploratory laparotomy was refused.

DIAGNOSTIC METHODS

An adequate history and physical examination are of the utmost importance and may immediately give a lead as to the cause of the precocious development. With only one exception, Case 4, those patients with virilization since birth were classified as adrenogenital syndrome on the basis of adrenocortical hyperplasia. This conclusion is also supported by Wilkins' recent review of the literature.[45, 46]

True or physiologic early puberty tends to occur after 4 or 5 years of age. A history of retarded mental development, convulsions, and other neurologic signs should make one suspect a central nervous system lesion.

Statural overgrowth is common to all types of precocious sexual development but may occasionally be absent. Obesity may suggest either a Cushing's syndrome or a hypothalamic lesion. Advanced bone growth by roentgenographic methods is also typical of most cases of precocious development, but it is usually more marked in the adrenogenital syndrome than in any of the other classifications, often exceeding the chronologic age by more than four years in these cases. Bone maturation is thus of considerable diagnostic value. In no instance in our patients was roentgenographic examination of the skull of any value; however, we do feel that this should constitute a part of the routine investigations since it may reveal evidence of a space occupying intracranial lesion.

Intravenous pyelography should be an important part of the examination in all children wherein an adrenal lesion is suspected, i.e., when virilization is present. In both of our patients with adenocarcinoma of the adrenals the lesions were visualized by this method. In spite of reports to the contrary, we feel that perirenal insufflation with air is a dangerous diagnostic procedure and should be used only in cases where a laparotomy is contraindicated. In the one case where perirenal insufflation was used in this series, death resulted shortly after the procedure from an air embolus (Case 9).

Glucose tolerance curves may be of aid in establishing the diagnosis of Cushing's syndrome. Few other blood chemical tests are helpful in our present state of knowledge.

Urine assays of estrogens, F.S.H., and 17-ketosteroids are of some value in these cases. F.S.H. is usually somewhat increased in amounts in lesions of the central nervous system,[40] Albright's syndrome,[2, 35] and early physiologic puberty.[27, 32] Estrogen levels were of relatively little value in our series of cases since the results were usually in the range that could be anticipated from the physical examination. In gonadal tumors such a determination might be of considerable aid.[5, 9, 10, 21] Assays of the 17-ketosteroids were usually found elevated to a moderate extent in adrenal hyperplasia and to a slight extent in other forms of precocious development. There was marked elevation of these excretion products in one of the two patients with an adrenal cortex adenocarcinoma but only slight elevation in the other. One might conclude that these tests are of value but that they should be interpreted with considerable caution.

Vaginal smears for cornification or glycogen content agreed essentially with estrogen levels and physical development. Because of the relative simplicity of technique, this procedure warrants more extended use.

Pneumoencephalograms are of value in localizing lesions of the brain but should be resorted to only after careful evaluation of the patient. Electroencephalograms were rarely of great aid to us in establishing a diagnosis.

In summary, it may be stated that a carefully obtained history and physical examination are of the greatest importance. Laboratory tests frequently offer little additional information except to support clinical observation.

Roentgenologic studies are of value in establishing a diagnosis of the adrenogenital syndrome from the standpoint of osseous maturation and tumors of the adrenals by pyelography. The period during which these studies were carried out has seen the establishment of more exact methods of diagnosis by laboratory measures; however, accurate clinical observation remains the most valuable diagnostic asset.

DISCUSSION

The development of sexual precocity has always excited considerable interest among clinicians, but only in relatively recent years has any order of classification of the etiological factors been made. The relative frequency of the different causes has not been very carefully evaluated. A review of the literature revealed few studies such as that presented in the present report.

Simple hyperplasia of the adrenal cortex leading to virilization has frequently been observed.[4, 8, 28, 31] Wilkins[45] reported seventy cases of the adrenogenital syndrome due to adrenal tumors in children under 12 years of age. This large number was collected from all the literature to 1949. Twenty-six of these children had Cushing's syndrome in association with virilism. One boy had an adrenal tumor causing feminization, the only one to be reported. Of the seventy cases, fifty-three occurred in females. In all of these cases the onset of symptoms followed birth. Therefore, our patient with precocious development from birth due to an adenocarcinoma of the adrenal is the first to be observed.

Melicow and Cahill[31] in 1950 reported on twenty children with the adrenogenital syndrome and stated that laparotomy revealed no obvious adrenal lesion in half of the patients. Only one of this series had a carcinoma and two patients were not explored. The actual incidence of this syndrome is not known but it is not rare.[40, 45, 46] This fact can be ascertained from the frequency with which it occurred in our series of thirty patients plus the large number that have been reported in the literature. It is more common in girls than in boys. Wilkins[46] states that when the condition is present at birth, it is always due to hyperplasia of the cortex, and when it occurs later in childhood, it is most likely to be due to adenoma or carcinoma. Our one case appears to represent an exception to this rule.

Chute and collaborators[8] reported a total of thirty-three cases of Cushing's syndrome in children up to 1949, many of which displayed some degree of virilization. The criteria used in making this diagnosis vary considerably and account for the varied number of cases reported by different authors.[12, 28] Our patient had most of the cardinal symptoms of the syndrome associated with virilism. These consisted of obesity of the trunk and neck, hypertension, and a diabetic glucose tolerance curve.

Treatment of these children with adrenal virilism represents a real problem. When hyperplasia is the cause in girls they are often maladjusted, and psychotherapy is certainly indicated for both patient and parents. In small boys the problem is also important but they usually grow up to their sexual development in due time. Estrogen therapy has been used in girls but its value is open to some question since it does not alter the primary pathology.[13] We have used it in one patient with very limited success. Amputation

of the clitoris and plastic operations have some merit in removing or modifying a source of physical and psychologic irritation. Incomplete adrenalectomy has proved disappointing in therapy as the remaining tissue also becomes overactive. Removing too much of the cortex leads to Addison's disease. Prognosis for life is generally good, although reports of congenital hyperplasia eventually leading to adrenocortical insufficiency have been made.[11, 49] None of our patients have shown such evidence during the period that they have been followed (from over one to nine years).

When either an adenoma or carcinoma is discovered, surgical removal is indicated. To reduce the possibility of acute adrenal insufficiency postoperatively, two precautions have been advocated:[17, 26] (1) administration of ACTH preoperatively to stimulate the contralateral adrenal cortex which is often atrophic, and (2) administration of cortical extract postoperatively until the remaining adrenal cortex assumes full physiologic activity. The operative mortality in the past has been about 50 per cent.[16, 17, 19, 26, 33] In our own two cases one is living and well four years following removal of a carcinoma and the other died postoperatively of pulmonary atelectasis.

A review of the literature gives little indication of how commonly lesions of the central nervous system are associated with sexual precocity. The causes may be varied and include hydrocephalus, encephalitis, meningitis, congenital anomalies, and brain tumors.[3, 7, 23, 40, 42, 44] In all cases the development has been isosexual and such lesions are stated to be more common in the male. Including the patient with the brain tumor, this group represented the second largest number of cases in our series, eight in all. Brain tumor as a cause of precocity is quite rare. Weinberger and Grant[44] collected from the literature a total of only seventeen cases to 1941. Bailey and co-workers[3] in an unselected study of 100 consecutive cases of brain tumors in children found only three associated with early sexual development. They further note that pineal tumors rarely cause precociousness and only in the male. Horrax[23] agrees with these observations. Some authors[42] would place Albright's syndrome in this classification since abnormalities in the vicinity of the mammillary bodies have been described in one case. Treatment of these patients is indeed difficult. Surgical removal of a tumor when present is seldom successful due to its inaccessible location. As previously noted in our patient and in the reports of Bronstein and associates[7] life may be prolonged in the face of a hypothalamic tumor. In those patients without evidence of brain tumor at the initial examination, careful observations should be continued as such tumors often lie in a relatively silent area so far as other signs or symptoms are concerned. Symptomatic treatment of associated convulsions is indicated in all cases.

It should be mentioned that a tumor of the pituitary has never been shown to cause precocious sexual development. This fact needs emphasis as it is contrary to what is generally believed. There is still considerable argument as to whether the primary lesion in Cushing's syndrome is in the pituitary or in the adrenal cortex.[1, 18, 37]

Early physiologic puberty was first described in some detail by Novak[32] and has been studied by others.[15, 22,

[27, 40] Often the only means of establishing such a diagnosis is by repeated observations and laboratory tests. Of some aid is the fact that these patients, more often girls than boys, do not show any additional abnormalities except advanced physical development of a moderate degree. Excretion of hormones or hormone products does not exceed normal adult levels. Occasionally, a family history of early development in either mother or father may be obtained. This was true in one of our girls whose mother had her menarche at 10 years of age and the patient at 8 years. Had a more thorough investigation along this genetic line been carried out in other cases, a higher degree of correlation might have been made.[46] It is obviously important to realize that these cases are not uncommon. Wilkins[47] found that approximately one-half of his patients with advanced development belonged to this category. We do not feel that hormone treatment is indicated to delay or alter development.[15] Follow-up observations on our patients have shown that the majority experience no particular difficulties after they and their parents have been reassured.

Simple breast hypertrophy was present in two cases and resembled those described by Talbot.[40] Bronstein and Cassorla[6] have furnished us with a good differential diagnosis of the condition. This may be outlined as follows according to etiology:

Hypertrophy of the newborn.
Adolescent hypertrophy (both sexes).
Endocrinopathies.
Estrogen and androgen therapy.
Cirrhosis of the liver.
Leucemic infiltration.
Tumors and cysts.
Simple breast hypertrophy (as here described).

No cases of primary gonadal involvement were encountered among our patients, unless one wishes to speculate that the mumps temporarily stimulated ovarian function in Case 18. Granulosa cell tumors of the ovary are exceedingly rare in children. A total of not over twenty cases have been reported to the present time.[5, 9, 10] Dargeon[10] reported on fourteen consecutive ovarian tumors seen in children. None of the patients had a granulosa cell tumor, and only one of the patients manifested any endocrine abnormalities. This was a 14-year-old girl who developed irregular menses. The most common symptom was a pelvic mass. Mason[27] quotes Novak as stating that only one granulosa cell tumor was observed at the Johns Hopkins Hospital in the last sixty years. This type of tumor produces false precocious puberty since the entire stimulating factor is the increased production of estrogens by the granulosa cells. Arrhenoblastomas of the ovary are masculinizing in effect and none have been observed in children under 15 years of age.[10] Dysgerminoma is also a rare tumor in children and has been associated with precocious sexual development in only two girls. In both of these the result was an isosexual development.[21] Teratomas and other ovarian tumors are uncommon in the pediatric age groups and rarely result in endocrine abnormalities.[9, 10] Assay of the urine for estrogens will reveal an extremely high output in the presence of a granulosa cell tumor, and the Friedman test is frequently positive in the presence of dysgerminomas.[21]

Kimmel[25] reported one case in which sexual precocity and statural over-

growth resulted from an ovarian cyst. When this was removed, all of the abnormal signs underwent rapid regression. Pathologic study of the tissue failed to explain adequately the cause of the endocrine abnormalities.

Neoplasms of the testes causing precocious development are as rare as similar ovarian dysfunctions.[14, 30, 38] Only eleven cases have been reported in children to the present time. The cell type in such tumors is believed to arise in the interstitial tissue. Surgical removal of such tumors is usually successful as metastatic spread is delayed.

CONCLUSIONS

1. A review of thirty children with precocious sexual development, each observed over a period of at least one year, revealed the most common cause (nine cases) to be the adrenogenital syndrome. Two patients with adenocarcinoma of the cortex were present in this group, one having had symptoms present at birth. Precocious development associated with lesions of the central nervous systems was second in frequency (eight cases). Only one of these patients had definite evidence of brain tumor and was alive seven and one-half years after the diagnosis was established although no specific therapy was attempted. Physiologic early puberty was the third most commonly encountered classification (seven cases). Other syndromes were relatively uncommon and included in the order of frequency: polyostotic fibrous dysplasia (two cases), benign breast hypertrophy (two cases), Cushing's syndrome (one case), and unclassified (one case). No cases with primary gonadal involvement were observed.

2. The first case of adenocarcinoma of the adrenal cortex causing symptoms of precocious development at the time of birth is reported.

3. There was a preponderance of females to males in our series in a ratio of nine to one. The explanation of this marked sex difference in an unselected group of patients is obscure.

4. A carefully obtained history and physical examination are of the greatest importance toward reaching a correct diagnosis. Laboratory methods should be interpreted with some caution and always in the light of clinical observations. The various diagnostic methods available are discussed and their proper evaluation is attempted.

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CLINICAL STUDY IN MAN OF THE EFFECTS OF VARIATION OF AGENIZED FLOUR PRODUCTS IN THE DIET

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AN EXTENSIVE series of investigations, well summarized and reported by Newell and associates[1] and Silver and collaborators[2] have clearly shown a toxic effect in various animal species fed white flour which had been bleached with nitrogen trichloride (known commercially as Agene). Of particular interest was the fact that a clinical convulsive state and electroencephalographic abnormalities could be induced in some of these animals when subjected to such materials in adequate amounts.

Because of this, investigations were undertaken at various institutions to see whether such agenized wheat products might have a similar effect in human beings. One of these studies was carried out on in-patients of the Emma Pendleton Bradley Home, a children's neuropsychiatric hospital.

EXPERIMENTAL PLAN

The basic project was to attempt to determine some possible effects of agenized flour upon human beings as might be manifested by changes resulting from its withdrawal and graded reintroduction into the diet of these children.

The individuals studied included all those patients residing at the Emma Pendleton Bradley Home who had an abnormal electroencephalogram, whether associated with epilepsy, brain damage, or behavior problems, as it was felt that these might be the most sensitive indicators of any toxic effect. There was a total of six with epilepsy, of various clinical types; three with the organic syndrome of behavior as described by Rosenfeld and Bradley[3]; and eighteen with behavior problems, either of the habit disorder or conduct disorder type. In addition, six children with normal electroencephalograms were added to serve as controls. The children were of both sexes and ranged from 7 to 13 years of age at the beginning of the project.

For all of these, continuous recordings during various stages of manipulation of agenized products in the diet were made as to biochemical changes, electroencephalographic changes, incidence of convulsions, and behavior.

The study covered a period of one year and was divided into two distinct but identical cycles of six months. For each of these cycles there was an initial period of one month during which the children were fed on a standard house diet, in which presumably 100 per cent of the flour products were agenized. This was called Phase I.

Performed under contract with the Medical Research and Development Board, Office of the Surgeon General, U. S. Army, Washington, D. C., and in cooperation with the Medical Nutrition Laboratory, Chicago, Ill., under the direction of Dr. Robert E. Johnson. The project dietitian was Miss Beatrice Watcke.

In Phase II, all agenized flour, in whatever form it might appear, was replaced by unbleached flour, which was specially milled.*

All edibles containing flour were prepared in the Bradley Home kitchen and bakery, and food, candy, etc., were not allowed from any outside source.

In Phase II, agenized products were gradually reintroduced into the dietary in graded amounts. This phase covered a period of two months. For the first two weeks 25 per cent of the flour products were agenized and the remainder was unbleached flour. For the next two weeks agenized flour made up 50 per cent of the flour intake; for the next two weeks, 75 per cent; and for the last two weeks 100 per cent agenized flour was used.

Out of this experimental group, three children stayed at the Home for a sufficiently long period so that they were included in both cycles of study.

METHODS

Behavior.—As part of the routine care and study of the children at the Bradley Home, for each patient detailed reports as to the child's behavior are made every two weeks, according to a standard outline, by representatives of each of the various kinds of staff members in daily contact with the children. These include medical staff, nurses, teachers, group leaders, and recreational workers. These reports deal with the behavior of the child in free play periods, in carrying out the various ward routines, in the dining room, in organized recreational activities, in arts and crafts, and in school.

So as not to introduce any outside suggestion or artifact, it was decided to utilize these regular reports rather than to prepare any special questionnaire which might hint at items to be given special attention. Study of these reports, therefore, provided the raw material for analysis of the children's behavior and any possible effects of varying amounts of Agene upon it.

Electroencephalography.—A standard technique was used throughout. All records were taken on an eight-channel Grass Model 3A machine. Electrodes were of the Grass silver cup type. They were placed in the frontal, parietal, occipital, and temporal regions on both sides and on both ears. Each recording included both hemispheric and comparison runs using scalp to ear linkages, with the ear leads both joined together and alternated. Scalp-to-scalp linkages along the hemispheres were also used. There was a standard period of hyperventilation of one and one-half minutes. All records were in the waking, resting state. The electroencephalograms were classified according to the method of Gibbs and Gibbs,[4] adjusted for this age range.

Dietary.—The dietary intake of each child on the study was followed as closely as possible. Standard servings were used, and these were weighed and measured so that at least a fair approximation of intake could be obtained by multiplying the number of servings consumed for the figure gotten for that particular standard serving. The diet was then calculated so that the following figures were obtained for each child for each day: Total calorie intake, total protein intake, proportion of this protein intake which was of animal origin and of other origin, fat intake, carbohydrate intake, and the percentage of the total caloric intake which was provided by flour and flour

*Supplied by Prof. Max Milner of Kansas State College, Manhattan, Kan.

products. These figures were not obtained by actual chemical analysis but by the use of standard dietary tables, so that some margin of error could have been introduced by the amount of cooking, etc. The cooking was supervised by the project dietitian in an attempt to make this as standardized as possible. In addition, all flour products were prepared in the Bradley Home kitchens by special personnel under the direction of the project dietitian.

Laboratory.—Laboratory procedures were designed for the study of hematopoiesis, kidney and liver function during the three phases previously outlined.

Preliminary studies were performed on all subjects prior to beginning the project to determine the normal values for each individual. The usual commercial bread was used as part of the diet during that period.

Unagenized flour was served during Phase II. Monthly laboratory studies were performed to note any deviation from the previous normal values and also possibly to set up a new set of normal values with unagenized flour.

During each of the four periods of increased agenized flour, laboratory studies were performed after allowing several days for the product to produce its effect.

Standard methods were utilized.[5] The hematopoietic function was evaluated by the complete blood count, hematocrit, sedimentation rate, blood cell fragility tests, and bleeding and clotting time.

The kidney function tests included complete urinalyses as well as blood urea nitrogen,[6] blood nonprotein nitrogen,[7] and blood creatinine.[8]

The liver function tests included icterus index,[9] blood glucose,[10] total protein with albumin-globulin ratio,[11] blood bilirubin,[12] cholesterol-cephalin flocculation,[13] prothrombin time,[14] bromsulphthalein excretion,[15] as well as urinary and fecal qualitative urobilinogen[16] and urinary porphyrins.[17]

RESULTS

Behavior.—There was no sudden or consistent alteration in behavior associated with manipulation of Agene. There was a slow but gradual decrease in difficult or aberrant behavior in most of the children throughout both phases of the Agene Project. Improvement was the same whether they were on or off Agene, presumably due to the effect of residence and treatment at the hospital. Introduction of Agene had no noticeable effect. Occasional marked changes of behavior were coincidental with introduction or removal of various medications or with variations in psychotherapy.

Convulsions.—There was neither increase nor decrease in the frequency of convulsions attributable to Agene.

Laboratory.—There were no changes in laboratory studies which were of a similar nature in both Cycle I and Cycle II. During Cycle I there was a pattern of slight elevation of blood urea nitrogen to high normal values with a corresponding average decline of total protein of 1 to 2 grams. This was only evident during the 25 per cent and 50 per cent agenization period. At these times it was the globulin which had decreased. Also, during the 50 per cent Agene period, five children had moderately positive cephalin flocculation reactions while five others had slightly positive values. During the same period, approximately one-third

of the children who previously had normal urine albumin values showed slight increases. These findings were not again noted in Cycle II, either in the entire group or in the three children who were studied during both cycles.

In Cycle II during the 25 per cent period, in eight cases the nonprotein nitrogen dropped suddenly to low limits of normal and gradually became elevated as Agene was increased. The drop in blood urea nitrogen was less dramatic but followed a similar pattern.

Electroencephalography.—There was much variation in the encephalographic picture during the various phases studied. Two children developed fast activity after the resumption of agenized flour in the diet, whereas there had been no fast activity in the preceding three-month period on completely Agene-free intake. One of these patients was also included in the second study cycle and here failed to demonstrate such fast activity when Agene was reintroduced. Both of these also fell in the group mentioned under "Laboratory" which demonstrated a decline in total protein at the time agenized flour was reintroduced. One of these had a normal cephalin flocculation reaction throughout. The other had a 2+ reaction during the preliminary period on house diet, a 2+ and then negative reactions in the three months without Agene and then a number of positives, including a 4+ and 3+ when Agene was reintroduced. These associated findings are of interest but it is hard to evaluate their significance.

Another patient had a very slow (S2) record while on the house diet. During the three months of Agene-free intake, he had a less abnormal, moderately slow (S1) record repeatedly. On 25 per cent and 50 per cent Agene intake his electroencephalogram was still moderately slow (S1); on 75 per cent Agene he had a mixture of moderately slow (S1) and moderately fast (F1). When finally returned to 100 per cent Agene intake, he again reverted to a very slow (S2) record. This child had no convulsive manifestations and was not receiving any anti-convulsant medication. This again may be just an interesting coincidence.

One patient whose record was previously normal briefly showed a moderately slow (S1) record after Agene was reintroduced into the diet. Another, a known convulsive, whose medications were being shifted, developed 3 per second spike wave complexes in the 25 per cent Agene period. These were replaced by spikes in the 50 and 75 per cent periods, but all paroxysmal discharges disappeared when 100 per cent agenized flour was being used.

On the other hand, in two cases paroxysmal discharges which were noted during the Agene-free period disappeared when Agene was reintroduced. Most striking was the fact that the remainder of the patients, by far the majority, failed to show any change whatsoever with all the shifts in agenized-flour intake which were made. This applied whether the pre-experimental electroencephalograms were normal or abnormal.

Despite some interesting individual correlations, therefore, in the study as a whole there seemed to be no consistent or significant change in the electroencephalogram associated with alterations in Agene intake.

DISCUSSION

The results presented show no significant changes in the various aspects

of the child population studied when agenized flour products were withdrawn from and reintroduced into their diet. This correlates well with the negative results in human beings of the complementary study of Newell and associates[1] in which agenized materials were fed in excessively high quantity.

Although the laboratory studies during the first cycle were suggestive of some possible relationship to Agene and protein metabolism, failure to duplicate these findings during the second cycle may point to a seasonal variation in protein, since there was no correlation between the fall of protein and the diet.[17]

Also, there was no evidence that Agene affected the body chemistry since during the Agene-free period there were no consistent alterations in normal laboratory values.

CONCLUSION

1. No toxic effects were noted following upon the removal and reintroduction of agenized flour products into the diet of a child population, many of whom were convulsives or had abnormal electroencephalograms.

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ACUTE GLOMERULONEPHRITIS: IMPETIGO AS AN ETIOLOGICAL FACTOR

A Review of 124 Cases at Lloyd Noland Hospital, Fairfield, Ala.

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MUCH has been written on the subject of acute glomerulonephritis since it was first described in 1836, yet our medical texts today continue to describe it much the same as did Richard Bright.[1] Little has been added to the description of the disease, but many volumes could be filled with the research that has been done in an attempt to clarify its etiology. Much of the current investigation has shown that there is probably an immunologic or antigen-antibody reaction which is invoked by an antecedent infection due to a strain of streptococci producing a so-called "nephrotoxic substance."[2, 3, 4, 5] It is not within the scope or the purpose of this review to discuss this intricate problem, but to present some clinical data which show a decided change in the incidence of certain antecedent infections.

In the six-year period beginning January, 1944, and ending December, 1949, there were 124 cases of acute glomerulonephritis admitted to the Pediatric Service of Lloyd Noland Hospital. It is the purpose of this review to reappraise the incidence of preceding infections in nephritis. A few other observations will be mentioned.

It was found that the infections preceding, or coexisting with, the nephritis fell into fifteen categories, as shown in Table I. As indicated, the most common antecedent infection was impetigo. Skin lesions are listed by most authors in the texts as being of relative minor importance.[2, 3, 4, 5] However, we have found the incidence somewhat greater than that of acute tonsillitis, which has always been considered the major offender. Another rather striking observation noted was the sharp increase in the number of skin infections preceding nephritis occurring after the widespread use of penicillin in 1945 and 1946.

It was noted that the average age was 6½ years. Only one child was under 1 year of age, and supported an honored axiom by having congenital syphilis.

The sex incidence, which is probably of no significance, showed a predominance of Negro males and white females, fewest cases occurring in Negro females. The average hospital admission was for nineteen and one-half days, the longest being forty-nine days and the shortest only four hours. The latter accounted for one of the two deaths, the picture being that of a rapidly fulminating disease with death approximately four days after onset of symptoms. The only other death was that of a 3-month-old

TABLE I. INFECTIONS PRECEDING ONSET OF ACUTE GLOMERULONEPHRITIS

ANTECEDENT INFECTION	NO. OF CASES	% OF TOTAL
Acute tonsillitis	39	31.45
U. R. I.	13	10.48
Impetigo	42	33.87
Pneumonia	6	4.83
Scarlet Fever	4	3.22
Rheumatic Fever	2	1.61
Diphtheria	1	0.8
Otitis media	1	0.8
Cellulitis	1	0.8
Infected burn	2	1.61
Congenital syphilis	1	0.8
Gastroenteritis	1	0.8
Balanitis	1	0.8
Mesenteric adenitis	1	0.8
None elicited	13	10.48

Note: Several of the above cases had more than one infection, consequently the total in per cent slightly exceeds 100.

Negro male, with congenital syphilis. The average length of illness before admission to the hospital was eighteen and one-half days, the longest being twenty-eight days, and the shortest twenty-four hours.

The presenting symptom in all but six of these cases was "swelling." This again represents a departure from the usual description of the disease, which emphasizes changes in the color and amount, or both, of urine as the most common initial complaint.[2, 3, 4, 5] In only two of the patients in this series was the presenting complaint that of bloody urine. Table II shows the statistics according to sex, color, length of hospitalization, duration before admission, and presenting symptoms.

Laboratory findings in all cases included the presence of albumin and red blood cells in the urine. Blood chemistry showed 40 per cent of the nonprotein nitrogen elevated, with 35 mg. per cent considered as the upper limit of normal. The average nonprotein nitrogen was 49.9 mg. per cent. Blood sedimentation rate determinations were elevated in 96 per cent, using the Cutter method with 10 mm. considered as the upper limit of normal.

The blood pressure was elevated in 107, or 86.4 per cent, of the cases, in some instances being as high as 180-190/110-120.

DISCUSSION

From an analysis of these 124 cases it is apparent that the percentage of skin infections noted is a marked departure from the etiological causes generally accepted. In our experience a full one-third of the patients admitted had a rather slow moving skin infection preceding the development of the acute nephritis. The child with a slowly progressing impetigo generally is not acutely ill, and usually runs no temperature. For this reason, he is often allowed to go for some time without any vigorous attempt at adequate treatment. In the

TABLE II

CASES						AVERAGE DAYS ILLNESS			PRESENTING SYMPTOMS AND SIGNS	
SEX		RACE		RESULTS						
M	F	W	N	RECOVERED	EXPIRED	HOSP.	PREHOSP.	POSTHOSP.		
75	49	64	60	122	2	19½	8½	*	Edema	118
									Convulsions	4
									Hematuria	2

*With few exceptions, posthospital nephritis cases are followed in the out-patient clinics until urinalyses, blood pressure, and sedimentation rates are normal, and the patient is clinically recovered. This convalescent period varies from several weeks to months.

past five years, the child with the acute febrile illness as evidenced by tonsillitis, otitis media, or other infections, is usually rapidly brought under control with penicillin, the sulfonamides, or other agents. It is thought that this fact may account for the change in incidence of skin lesions as an antecedent to acute glomerulonephritis, and that more prompt and vigorous attention to impetigo and other skin infections in children may further reduce the incidence of acute glomerulonephritis.

Except for the changing incidence of impetigo and skin infections as a preceding infection in acute glomerulonephritis, and the frequency of edema rather than hematuria as a presenting symptom, little change has been noted in this series in the general picture of acute glomerulonephritis. In general, the study of the patients has become more complete. Except for the use of penicillin routinely to combat coexisting infections, or possible foci of infection not found on examination, there have been no changes in the treatment. The overall mortality seems to have remained quite constant through the years—an almost irreducible 1.5 per cent.

SUMMARY AND CONCLUSIONS

1. One hundred twenty-four cases of acute glomerulonephritis at Lloyd Noland Hospital from January, 1944, to December, 1949, are reviewed.

2. The most common antecedent infection was found to be impetigo, which occurred in forty-two, or 33.8 per cent, of the cases. This represents a definite departure from the usual statistics which list acute tonsillitis as being the most common antecedent infection, and relegate skin infection to a place of minor importance.

3. It is suggested that the increased use of penicillin and other agents to rapidly control tonsillitis and other acute febrile illnesses, while the so-called "innocuous" skin infections such as impetigo are often not so vigorously treated, may account for this changing incidence of antecedent infection.

4. It is urged that more prompt and vigorous treatment be instituted in those cases of impetigo not responding quickly to local measures, and suggested that such vigorous treatment may result in a lower incidence of acute glomerulonephritis.

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A SURVEY OF THE Rh PROBLEM IN MIXED RACIAL GROUP

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THE discovery of the Rh factor, in 1937,[1, 2] inevitably led to intensive investigation of its role in human immunology. There resulted the development of knowledge of intragroup hemolytic reactions[3] and of the causes of certain stillbirths[4] and hemolytic disease of the newborn.[5, 6] The production of Rh antibodies by the Rh-negative woman, the transfer of these antibodies to produce hemolytic disease in the Rh-positive offspring, and the use of replacement transfusion as dramatic, lifesaving therapeusis have all been dealt with repeatedly in experimental and statistical studies.[7, 8, 9, 10, 11]

The racial populations seen at the Lincoln Hospital, comprising white, Negro, and Puerto Rican, afforded large and interesting groups for analysis. The purpose of this paper is, therefore, to survey the "Rh problem" in this mixed group, with a view to determining the incidence of Rh negativity and of hemolytic disease of the newborn.

MATERIAL FOR ANALYSIS

The material for analysis is a group of 3,011 completed pregnancies seen at the Lincoln Hospital during the seventeen-month period from May 20, 1947, to Oct. 31, 1948. These pregnancies represent all of the patients delivered during the period who had been registered with the hospital's Prenatal Clinic. Nonclinic patients who appeared for delivery only are not included. Also excluded from consideration and from the statistics is one Chinese woman, the only one of her race seen during the study period. Clinic attendance was the only basis for selection of patients for this study.

METHODS OF STUDY

Each patient who presented for prenatal care was Rh tested with anti-D (Rh_0) serum by the tube method. The resultant Rh-negative groups formed the nucleus for further analysis.

Immediately upon delivery of an Rh-negative mother (or of any mother whose Rh status was momentarily undetermined), a cord blood specimen was obtained for study. As soon as possible thereafter, Rh typing and either a conglutination test,[12] or, later in the study, a Coombs test,[13] were performed. The infant was immediately examined and followed closely for any evidence of the disease. Where serologic and/or clinical evidence was found, a complete hemogram was done on the infant's capillary blood. Decision as to diagnosis was then made.

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RESULTS OF STUDY

In the statistical presentation, we have differentiated among the three races which comprise the patient group, and this breakdown will be seen in the accompanying tables.

TABLE I. RESULTS OF Rh TESTING (MIXED RACIAL GROUP OF 3,011 WOMEN)

	WHITE	NEGRO	P.R.	TOTAL
Number of patients	582	1,301	1,128	3,011
Rh-negative women	91	148	144	383
Per cent Rh-negative women	15.6	11.4	12.8	12.7

Rh Testing.—Table I demonstrates the results of the Rh testing of all the mothers in this group. It may be seen from the table that, in the entire group, Rh negativity was found in 383, or 12.7 per cent. Among 582 white women, the incidence was higher, 91 or 15.6 per cent. Among 1,301 Negro women, it was appreciably lower, 148 or 11.4 per cent, whereas the Puerto Rican group (1,128) occupied an intermediate position, almost at the average (144 or 12.8 per cent).

Results of Pregnancy.—Table II records the results of the pregnancies of all 383 Rh-negative women of this series. Three white, three Negro, and one Puerto Rican neonates were obvious cases of hemolytic disease of the newborn. There were six stillbirths in this group of deliveries. In all but one of these, it was impossible to obtain cord or other blood for study, and it was necessary to rely upon the clinical history of the mother's present and previous gravidity, and upon serologic determinations on the mother's blood. In only two cases, both white, were we satisfied that hemolytic disease was present.

TABLE II. RESULTS OF PREGNANCIES OF 383 Rh-NEGATIVE WOMEN

	WHITE	NEGRO	P. R.	TOTAL
Normal newborn	85	141	140	366
Abortions	0	1	1	2
Stillbirths	3	2	1	6
Neonatal deaths, extraneous	0	1	1	2
Hemolytic disease of newborn	3	3	1	7
Totals	91	148	144	383

TABLE III. CORRECTED INCIDENCE OF ERYTHROBLASTOSIS

	WHITE	NEGRO	P. R.	TOTAL
Number of cases	5	3	1	9
Number of Rh-negative mothers	91	148	144	383
Number of mothers	582	1,301	1,128	3,011
Incidence in all cases	1:116	1:434	1:1,128	1:335
Incidence in Rh-negative mothers	1:18	1:49	1:144	1:42

Table III, therefore, shows the corrected incidence of hemolytic disease of the newborn in the group tested. There were nine cases—five in the white, three in the Negro, and only one in the Puerto Rican race. In the entire group of 3,011 pregnancies, hemolytic disease of the newborn occurred in 1 out of 335 cases, with racial spread as follows: 1:116 among whites; 1:434 among Negroes; 1:1,128 among Puerto Ricans. Among Rh-negative women, the incidence was 1 out of 42; 1:18 for whites, 1:49 for Negroes, and 1:144 for Puerto Ricans. Of the seven live births, four were treated by exsanguination-replacement transfusion, and no treatment was required in the other three cases. There were no deaths.

DISCUSSION

Incidence of Rh Negativity.—Statistical comparisons of the incidence of Rh negativity must be viewed in the light of population differences. The figures in Table IV demonstrate these differences. Among the white population, our findings were in close agreement with a sampling of previous reports,[14, 15, 16, 17] despite the fact that our test group was such as to make the white subgroup relatively small (582). The largest previous group, that of Tisdall and Garland[17] (22,133 tests), contained 14.2 per cent Rh negatives.

TABLE IV. COMPARISON OF STATISTICS—INCIDENCE OF Rh NEGATIVITY

	WHITE (%)	NEGRO (%)	P. R. (%)
Lincoln group	15.6	11.4	12.8
Wiener[14]	12.9		
Potter[15]	15.0		
Potter[16]	14.0		
Tisdall and Garland[17]	14.2		
Landsteiner and Wiener[18]		8.0	
Levine[19]		4.5	
Tisdall and Garland[17]		9.89	
Santos and Stepto[20]		15.0	
		19.0—men 14.5—women	
Wiener[21]			10.1

There appears to be considerable variation in reports on the Negro race. Landsteiner and Wiener[18] reported 8.0 per cent Rh negatives in a group of 113 subjects. Levine[19] reported 4.5 per cent negatives among 264 subjects tested. Tisdall and Garland,[17] in 283 tests, found 9.89 per cent negatives. The most interesting survey is that of Santos and Stepto[20] who, in Chicago, found not only a much higher incidence of Rh negativity (15 per cent) in 1,000 samples, but a marked sex difference. Among 116 males, they found 19.0 per cent negatives; among 884 females, they found 14.5 per cent negatives. In view of the supposed lack of sex relationship, this is hard to understand. Our group, with 1,301 females, revealed 11.4 per cent Rh negatives.

Figures are scarce for the Puerto Rican population. Wiener[21] quotes unpublished statistics of 10.1 per cent Rh negatives out of 179 determinations. Our group revealed an incidence of 12.8 per cent Rh negatives. In this group, a low economic group recently arrived here, the median position between the white and Negro races tends to confirm Wiener's impression as to the admixture of these races in the Puerto Rican population.

Incidence of Hemolytic Disease of the Newborn.—Our initial impression as to the comparative infrequency of hemolytic disease of the newborn at the Lincoln Hospital was confirmed by the results of this study. Our total incidence of hemolytic disease was 1 in 335 births, considerably lower than that reported by other observers. Potter[15] reported an incidence of 1:252, and later[16] an incidence of 1:180 births. Wiener[21] reported an incidence of 1:250 births. These figures, for comparison with ours, are shown in Table V. Analysis of the figures

TABLE V. COMPARISON OF STATISTICS—INCIDENCE OF HEMOLYTIC DISEASE OF THE NEWBORN

	Rh-NEGATIVE MOTHERS (%)	INCIDENCE IN Rh-NEGATIVE MOTHERS	INCIDENCE IN ENTIRE GROUP
Potter[15]	15	1:37	1:252
Potter[16]	14	1:26	1:180
Wiener[21]			1:250
Lincoln Group			
Total	12.7	1:42	1:335
White	15.6	1:18	1:116

by race, however, reveals that the Negro and Puerto Rican groups account for the lowered incidence, whereas the white group alone bears a higher incidence than that previously reported.

The nature of the population studied influenced this distribution. The dwindling white population (and its Rh-negative component) is older and more parous than are the other races. The Puerto Rican group contained 44 per cent primiparas. The Negro group contained over 50 per cent primiparas. The white group had only 24 per cent primiparas. The increased incidence of Rh positivity among the Negro and Puerto Rican groups as contrasted with the white group is a second factor in the lowered incidence of the disease in these races. Other factors undoubtedly exist, but this study permits no more than speculation as to their nature.

SUMMARY

Three thousand eleven pregnancies were followed from presentation to post-partum period, for determination of the incidences of Rh negativity and of hemolytic disease of the newborn. Rh testing and adequate diagnostic measures applied to the offspring of these mothers were employed. In this group, a mixed white, Negro, and Puerto Rican group, accurate figures on the incidence of Rh negativity were obtained. Only nine cases of hemolytic disease were detected, of which two were stillbirths. The latter were the only deaths.

CONCLUSIONS

1. In the present series, Rh negativity occurred among white women at the rate of 15.6 per cent, among Negroes at the rate of 11.4 per cent, and among Puerto Ricans at the rate of 12.8 per cent.

2. In this series, the incidence of hemolytic disease of the newborn was 1:116 white births, 1:434 Negro births, and 1:1,128 Puerto Rican births, an over-all incidence of 1:335 births.

We are greatly indebted to Dr. Peter Vogel for his expert guidance throughout the study. Mr. Ernest Wunderlich performed most of the serologic studies.

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AORTIC ATRESIA WITH HYPOPLASIA OF THE LEFT HEART AND AORTIC ARCH

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THE application of surgical methods to the amelioration of certain varieties of congenital heart disease has emphasized the importance of accurate clinical and pathological observation, classification, and diagnosis in this field of study. Attempts at corrective surgery have been made not only in tetralogy of Fallot but also in other severe cyanotic lesions such as transposition of the great vessels.[4] The possible application of surgical procedures to young infants provides reason for further study of types of congenital heart disease which are considered incompatible with life beyond infancy. For this reason it seems worth while to report four infants with atresia of the aortic valve associated with hypoplasia of the left side of the heart who have been observed at The Children's Hospital of Philadelphia.

The combination of congenital anomalies found in these four patients (Fig. 1) includes (1) atresia or stenosis of the aortic valve of a degree sufficient to prevent the egress of more than a minute amount of blood from this orifice; (2) hypoplasia of the left atrium, mitral valve, left ventricle, and arch of the aorta; (3) hypertrophy and dilatation of the right atrium, right ventricle, and pulmonary artery; (4) a functioning patent ductus arteriosus; (5) a patent foramen ovale or some other anomalous pathway[3, 16] for the transport of blood from the left to the right atrium. A patent foramen ovale is usually but not invariably present. The hypoplastic mitral valve is otherwise normally formed.

It is extremely difficult to estimate from the literature the incidence of this complex congenital malformation. In many cases there are additional abnormalities and variations complicating the classical picture. The outstanding cause for confusion resides in variations in terminology due often to difference of opinion as to the primary or causative lesion. Instances of this anomaly have been described as congenital aortic atresia,[2, 5, 13, 24, 28, 30, 32, 33, 34] with hypoplasia of the left ventricle,[1, 21] congenital aortic stenosis,[15, 18] left-sided stenosis of the heart,[19] congenital mitral atresia,[14] coarctation of the aorta,[9] congenital myocarditis,[26] or endocarditis.[20] Errors in diagnosis even at the post-mortem table lead to further misunderstanding as to incidence. As Monckeberg[17] and others[2, 7, 23] have pointed out, instances of hypoplasia of the left ventricle associated with aortic and/or mitral atresia have not uncommonly been classified incorrectly as cases of cor biatrium triloculare due to the fact that the left ventricle consists of a minute cavity embedded in the mus-

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culature of the main ventricle and often can be demonstrated only by careful dissection. Monckeberg, for example, describes two such hearts at first considered to possess only a single ventricle in which a study of serial sections of the entire heart revealed the presence of a small, slit-shaped left ventricular cavity.

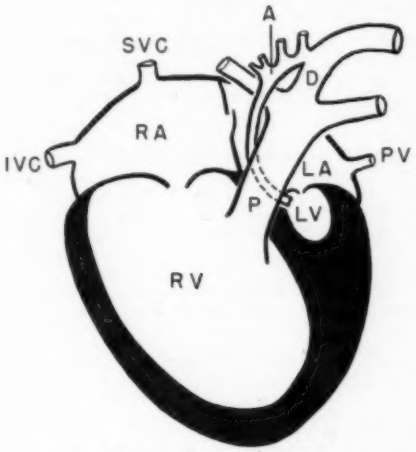

Fig. 1.—Diagram illustrating the combination of congenital anomalies found in association with aortic atresia and hypoplasia of the left heart. *A*, Aortic arch; *D*, patent ductus arteriosus. The aorta may arise from the left ventricle as pictured or may terminate blindly within the muscle mass above and to the right of the left ventricular cavity.

A careful search of the literature reveals several categories of abnormal hearts which are similar in many respects but nevertheless different. One such group consists of those hearts in which the primary lesion appears to be in the mitral valve. In these cases the mitral valve is grossly deformed or absent resulting in hypoplasia of the left ventricle, aortic valve, and ascending aorta. These latter structures are small but anatomically preserved. In another large group both the aortic and mitral valves are grossly deformed and the passage of blood through either orifice is impeded. Under these circumstances neither of the valves is merely hypoplastic but both show marked structural deformities. The clinical differentiation of either of these two pathologic varieties of congenital hypoplasia of the left heart from the type exemplified by our cases is impossible. For the sake of simplicity, we have included in this report only those cases in which the aortic valve deformity is the major defect and in which the mitral valve and left ventricle are anatomically intact but hypoplastic. Our review of the literature uncovered only thirty previously reported cases complying with these criteria. These are listed in Table I. Cases of congenital aortic stenosis associated with hypertrophy of the left ventricle and of mitral atresia or stenosis with or without aortic atresia will be discussed in subsequent reports.

Those investigators who have attempted to evaluate the etiology of this combination of congenital anomalies have in the main proposed two possible mechanisms to explain its origin. One of these suggests that the malformation results from intracardial infection during an early formative stage of the embryo. The conventional evidence presented in support of this concept takes the form of microscopic sections of myocardial tissue demonstrating infiltration of the cardiac muscle fibers with cells assumed to be of inflammatory origin plus some fibrous tissue overgrowth. Farber and Hubbard[10] offered a series of such histopathologic pictures considered by them to be suggestive of antecedent infection. These authors regarded the appearance of the lesions to be too old to be explained on the basis of postnatal infection since most of their pa-

TABLE I. DATA ON THIRTY-FOUR CASES OF AORTIC ATRESIA WITH HYPOPLASIA OF THE LEFT HEART*

AUTHOR	AGE	SEX	HEART SIZE†	FORAMEN OVALE	AORTIC VALVE	COMMENTS
1. Anderson and Sano[1]	3 da.	M	39.5 Gm.	Functionally closed	Fused leaflets	
2. Baggenstoss[2]	5 da.	M	30 Gm.	Functionally closed	Fused leaflets	
3. Canton[5]	2 da.	F	Normal	Patent—large	Membranous diaphragm	
4. DuShane[8] (Case 2)	4 mo.	F	Large	Patent—small	Membranous diaphragm	Right axis deviation in the electrocardiogram
5. Evans[9] (Case 25)	4 da.	M	--	Patent—large	Fused leaflets	
6. Evans[9] (Case 27)	3 da.	F	--	Patent	Fused leaflets	Left vertebral artery arising from aorta
7. Friedman, Murphy, and Ash (Case 1)	1 da.	M	21 Gm.	Patent—6 × 4 mm. in diameter.	Blind ending	
8. Friedman, Murphy and Ash (Case 2)	5 da.	M	36 Gm.	Patent—3 × 4 mm. in diameter	Blind ending	Left bundle branch block (terminal)
9. Friedman, Murphy, and Ash (Case 3)	17 da	M	26 Gm.	Closed	Nodular excrescence	Right axis deviation in the electrocardiogram
10. Friedman, Murphy, and Ash (Case 4)	2 da.	M	44 Gm.	Functionally closed	Nodular excrescence	Right axis deviation in the electrocardiogram
11. Isaacson, Spatt, and Grayzel[13]	2 da.	M	18 Gm.	Patent—5 mm. in diameter	Fused leaflets	
12. Large[14] (Case 2)	2 da.	M	39 Gm.	Patent—7 mm. in diameter	Fused leaflets	
13. Loeser[15]	2 da.	F	Large	Patent	Membranous diaphragm	
14. Monckeberg[18]	3 da.	M	Large	Patent—6 × 2.5 mm. in diameter	Membranous diaphragm	
15. Mueller[19] (Case 1)	5 da.	M	Large	Patent—small	Nodular excrescence	
16. Owen and Kingsbury[20] (Case 1)	12 da.	M	47.5 Gm.	Patent	Fused leaflets	
17. Popjak[21]	2 da.	F	--	Patent	Nodular excrescence	
18. Shattock[24]	25 da.	-	--	Patent	Membranous diaphragm	No cyanosis until ninth day of life
19. Stiassy[26]	4 da.	M	Very large	Closed	Nodular excrescence	
20. Summons[27] (Case 11)	15 wk.	M	Large	Patent	Fused leaflets	
21. Taussig[28] (Case 1)	2 da.	M	Very large	Patent—large	Fused leaflets	Small interventricular septal defect with overriding aorta
22. Theremin[29] (Case 81)	5 da.	M	--	Patent—5 mm. in diameter	Fused leaflets	
23. Theremin[29] (Case 82)	--	-	--	Patent—4 mm. in diameter	Fused leaflets	
24. Theremin[29] (Case 85)	--	-	--	Patent—4 × 2 mm. in diameter	Fused leaflets	

TABLE I—CONT'D

AUTHOR	AGE	SEX	HEART SIZE†	FORAMEN OVALE	AORTIC VALVE	COMMENTS
25. Theremin[29] (Case 87)	4 da.	F	Large	Patent—1 × 5 mm. in diameter	Fused leaflets	
26. Theremin[29] (Case 88)	2 da.	M	Normal	--	Fused leaflets	
27. Theremin[29] (Case 89)	5 da.	F	--	Patent—8 mm. in diameter	Blind ending	Fenestrated valve of patent foramen ovale
28. Theremin[29] (Case 90)	8 da.	M	Large	Patent—4 mm. in diameter	Fused leaflets	Right aortic arch
29. Theremin[29] (Case 92)	2 da.	F	--	Closed	Blind ending	
30. Von Haam and Hartwell[30] (Case 2)	12 da.	F	27 Gm.	Patent—14 mm. in diameter	Membranous diaphragm	
31. Wesson and Beaver[32]	2 da.	M	34 Gm.	Patent—large	Fused leaflets	
32. Wiglesworth[33]	18 da.	M	65 Gm.	Patent—2 mm. in diameter	Membranous diaphragm	
33. Willer and Beck[34] (Case 1)	3 da.	M	Large	Patent—4 × 2.5 mm. in diameter	Membranous diaphragm	Three porous defects in interauricular septum
34. Willer and Beck[34] (Case 2)	4 da.	M	Large	Patent	Fused leaflets	Accessory spleen and right renal cyst

*Cases of aortic atresia with associated mitral valve involvement other than simple hypoplasia have been excluded.

†According to Coppoletta and Wolbach,[6] the normal heart weight is 17 to 19 grams from birth to 3 week of age.

tients died within the first few days of life. In 1941, Paul Gross[11] reviewed the concept of fetal endocarditis and concluded that the occurrence of this entity had never been established. The case report used by Gross to illustrate his point of view was one of aortic and mitral stenosis with hypoplasia of the left ventricle. After careful microscopic study of this heart and a review of the literature, he expressed the belief that the genesis of these lesions was noninflammatory. The possible syphilitic origin as proposed by Warthin[31] can almost certainly be discarded.

The second theory of etiology for this combination of congenital anomalies holds that a developmental error occurs during the complicated process of formation of the normal four-chambered heart from its single hollow tube origin. Such defective development may arise from an imperfect germ cell or perhaps may result from some disturbance occurring during the course of organogenesis. The rather constant, almost predictable, pattern assumed by congenital cardiac anomalies, especially the one under discussion here, could more easily be attributed to developmental error rather than the haphazard effects of infection. However, it is probably correct to consider infection as one of the many agents capable of inciting developmental errors. The recognized association of maternal rubella in the first trimester of pregnancy with the occurrence of congenital anomalies is a strong point in favor of this hypothesis.

It was the view of Monckeberg[17] that congenital aortic stenosis or atresia was due to abnormal deviation of the septum which separates the common truncus arteriosus into the aorta and pulmonary artery during the period when torsion of the bulbus cordis occurs. He points out that in aortic atresia the relation of the aorta and pulmonary artery often varies from the normal although complete transposition occurs only rarely. The most common variation is one in which the small ascending aorta lies to the right, parallel with and posterior to the pulmonary artery.

CASE REPORTS

CASE 1. (J.W.).—*Atresia of aortic valve; hypoplasia of left heart and aortic arch; dilated pulmonary artery; hypertrophy and dilatation of right atrium and right ventricle; patent foramen ovale; edema and congestion of all viscera; subcapsular hematoma of liver; patchy atelectasis.*

This white male infant was born at home and was pronounced dead upon arrival at the hospital at the age of 24 hours. A post-mortem roentgenogram of the chest revealed enormous enlargement of the heart both to the right and left of the sternum.

At necropsy the skin was diffusely cyanotic and the face seemed edematous. Significant abnormalities were noted only in the heart with secondary changes in the viscera due to congestion.

The transverse diameter of the thorax was 10 cm. and of the heart 6 cm. The heart weighed 21 grams. The pulmonary artery arose normally. It was greatly dilated, while the ascending aorta was very small, lying posteriorly to the right and parallel to the pulmonary artery. The ductus arteriosus was so widely patent that the thoracic aorta seemed to be a continuation of the pulmonary artery with the two main pulmonary vessels resembling subsidiary branches. The aortic arch was of small caliber. Its diameter was greatest at the junction with the ductus, tapering to its smallest width as the base of the heart was approached. The vessels to the head and neck arose in the usual fashion. The great veins entered normally, but were extraordinarily large and distended with blood.

As viewed before opening, the heart was enlarged in its transverse diameter, the greater part of its mass being composed of right atrium and of right ventricle, which formed the cardiac apex. The right atrium was hypertrophied and dilated. The foramen ovale was only partly closed. When stretched, it revealed a tube-shaped opening with diameter 6 x 4 mm. at the distal end permitting a passage of blood only from right to left. The circumference of the tricuspid valve was 4 cm. Its anterior cusp was larger than the other two. The right ventricle was hypertrophied and dilated, with a markedly prominent pulmonary conus. The thickness of its wall in the dilated state was 4 mm. The interventricular septum was intact. It lay at right angles to its usual position so as to close off a small space in the upper posterior portion of the ventricular wall which formed a nonfunctioning left ventricle. The pulmonary valve was normal, with a circumference of 2.5 cm. The pulmonary artery presented a spindle-shaped dilatation above the pulmonary ring, the circumference of which was 1.8 cm. The circumference of the ductus arteriosus was 0.8 cm. The left atrium was very small. The mitral valve was a minute structure with two small fused cusps attached to fine, delicate papillary muscles. Its circumference was 1 cm. The left ventricle consisted of a tiny, empty, endocardial-lined slit with a wall 0.8 cm. thick. There was no aortic valve. The ascending aorta appeared as a thin-walled tube which terminated blindly in the ventricular muscle. The circumference of the ascending aorta was 0.2 cm; the transverse arch 0.5 cm., and the thoracic

aorta below the entrance of the ductus 1.6 cm. Two coronary arteries were given off normally, each having a diameter equal to that of the aorta.

The liver was greatly enlarged, extending 5 cm. below the right costal margin. The weight was 110 grams.

This white male infant, aged 5 days at death, was born at full term to a 22-year-old healthy primapara following an uneventful pregnancy. The father was 26 years of age and apparently healthy. The infant weighed 2950 grams, and was cyanotic for some un-

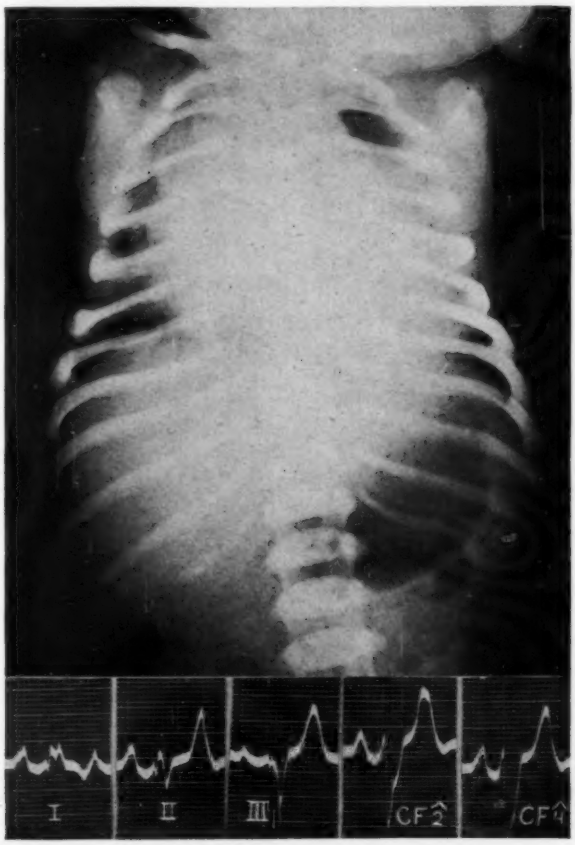

Fig. 2 (Case 2).—The roentgenogram shows massive cardiac enlargement with fulness of the pulmonary segment. The electrocardiogram taken shortly before death shows left bundle branch block.

CASE 2 (S.B.).—*Aortic atresia with hypoplasia of left heart and aortic arch; dilated pulmonary artery; dilatation and hypertrophy of right atrium and right ventricle; small patent foramen ovale; patent ductus arteriosus; fusion of two cusps of pulmonary valve.*

determined period of time immediately after birth. Cyanosis cleared for the succeeding thirty hours only to return intermittently and to become continuous on the fourth day of life. At this time a rapid respiratory rate and failure to swallow properly were also observed. On the fourth day of life

the patient was transferred to The Children's Hospital of Philadelphia. On admission the infant had a cyanotic tinge to the skin and mucous membranes of the entire body. The respiratory rate was rapid. There was a loud, blowing systolic murmur best heard in the fourth interspace to the left of the sternum. The heart was enlarged to percussion. None of the abdominal organs seemed enlarged. The hemoglobin was 15 Gm., erythrocytes were 4,950,000, and leucocytes 14,400. There were 68 per cent neutrophiles and 32 per cent lymphocytes. A blood culture was sterile after six days' incubation. The patient died nine hours after admission, having remained cyanotic and dyspneic throughout.

Roentgen Findings. (Fig. 2).—There was massive cardiac enlargement both to the right and left of the midline with fulness of the pulmonary segment. The lung fields were almost completely hidden by the cardiac silhouette. *Electrocardiogram*: The only tracing taken was recorded when the patient was in a terminal state. It showed a heart rate of 58 per minute with a P-R interval of 0.24 second. There was notching of the QRS complexes in all leads and a left bundle branch block. The T waves were diphasic in Lead I, tall and upright in Leads II and III. The P waves were wide, indicating auricular enlargement.

Necropsy examination was limited to the heart and lungs. The heart weighed 36 grams and presented the general appearance described in Case 1 with predominant enlargement of the right heart and pulmonary artery associated with hypoplasia of the left heart and aortic arch. The cusps of the pulmonary valve were thickened and two cusps were fused. When the atrial wall was stretched the foramen ovale presented a small opening 3 x 4 mm. in size. The left atrium was very small with a small appendage. The cavity of the left ventricle was about the size of a lemon seed. The mitral valve presented two small thickened cusps attached to minute papillary muscles. The aorta ended blindly in the heart muscle. The coronary arteries arose normally. The following measurements were noted: circumference of tricuspid valve 4.5 cm; pulmonary valve 2.5 cm; pulmonary artery 2.7 cm; ductus arteriosus 1.5 cm; ascending aorta 0.5 cm; transverse arch 0.5 cm; thoracic aorta below the origin of the ductus 2.5 cm.

CASE 3 (T.B.).—*Aortic atresia; hypoplasia of left heart and aortic arch; dilatation of pulmonary artery; dilatation and hypertrophy of right atrium and right ventricle; patent ductus arteriosus; closed foramen ovale; edema and congestion of lungs and abdominal viscera.*

This white male infant, aged 17 days at death, was born at term after a brief labor and precipitous delivery. Both parents were 35 years of age. Four other siblings were living and well. The mother was known to have had a basal systolic murmur from the age of 14 years. The birth weight was 2,900 grams. The infant was cyanotic for a few minutes after birth, but his color apparently responded to oxygen administration and suctioning of the upper respiratory tract. Cyanosis was noted again at 14 hours of life and persisted. A diagnosis of atelectasis was made at the maternity hospital based on a roentgenogram and fluoroscopic examination of the chest. After transfer to The Children's Hospital of Philadelphia at the age of 35 hours, the infant remained cyanotic in oxygen, and cyanosis was noted to become exaggerated by exertion. A constant soft blowing systolic murmur was audible in the second left interspace and under the left clavicle. The presence of atelectasis was confirmed and the condition treated with frequent stimulation, antibiotics, and oxygen. There was a gradual improvement in the infant's ability to feed, and the pulse rate diminished from 160 per minute to 120 per minute. The cyanosis, however, persisted. There was no evidence

of congestive failure, and the infant was sent home on the tenth day of life. The urinalysis on admission was negative. The blood count revealed a hemoglobin level of 20.5 Gm., with an erythrocyte count of 5,460,000. The leucocyte count was 6,500 with a differential count of 59 per cent neutrophiles, 37 per cent lymphocytes, and 4 per cent monocytes. The patient returned to The Children's Hospital of Philadelphia eight days later in a markedly dehydrated state, with oral thrush, intensely cyanotic, in marked respiratory distress, and died eight hours later. He had taken his feedings poorly during the three days prior to his demise and had become progressively more lethargic. On his first admission, this infant was thought to have two conditions, neonatal atelectasis which cleared with conservative handling, and a congenital malformation of the heart with gross intracardiac venous-arterial shunt. During the last four hours of life there was clinical evidence of congestive heart failure.

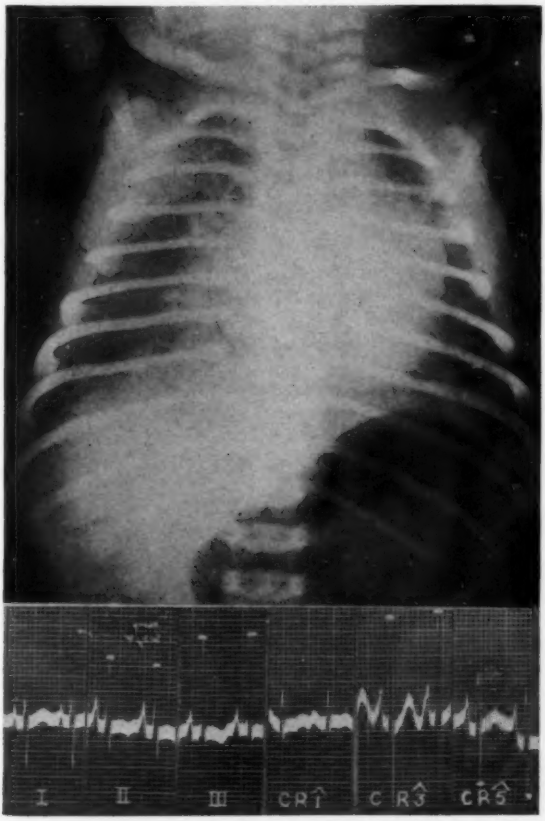

Fig 3 (Case 3).—The roentgenogram taken on the tenth day of life shows only minimal cardiac enlargement, noted especially in the pulmonary region. The right border of the cardiac shadow has been retouched. Lung fields show prominent vascular shadows. The electrocardiogram shows right axis deviation with inversion of T waves in Leads II and III and high P waves. Amplitude of T waves in CR_5 less than that in CR_1.

Roentgen Findings (Fig. 3).—Chest films taken at the maternity hospital during the first day of life revealed atelectasis and a small heart of normal contour. The cardiac silhouette on the tenth day of life had remained normal in size by x-ray and fluoroscopic examination, except for enlargement of the pulmonary segment. The atelectasis had cleared. No films were taken in the course of the final admission. The *electrocardiogram* showed right axis deviation with inversion of T waves in Leads II and III. The T waves were upright in the precordial leads, but of lower amplitude in lead CR_5 than in CR_3.

Necropsy revealed no abnormalities except in the heart, with secondary changes in the lungs and abdominal viscera due to congestion and edema. The heart weighed 26 grams. On inspection the heart and great vessels presented the appearance described in Case 1, with markedly distended veins, small aortic arch, and dilated pulmonary artery connected by a patent ductus to a large descending aorta. The right atrium and right ventricle were dilated and hypertrophied. The foramen ovale was completely closed. The left atrium was small but its appendage was dilated to a size 4 x 1.5 cm. as compared with 1 x 1.5 cm. for the appendage of the right atrium. The left ventricle was situated in the superior posterior portion of the ventricular mass, consisting of a diminutive chamber with hypertrophied wall. The mitral valve was small with two normal-appearing diminutive cusps. The aorta terminated in a nodular lesion through which no probe could be passed. The coronary arteries arose in the usual fashion from the small aorta.

The following measurements were noted: circumference of tricuspid valve, 4.2 cm; pulmonary valve 2.5 cm; mitral valve, 1.3 cm. The thickness of the wall of the right atrium was 0.4 cm; right ventricle, 0.7 cm; left atrium, 0.4 cm; left ventricle, 1 to 2 cm. The circumference of the pulmonary artery as it left the heart was 2.0 cm; of the ductus, 1.0 cm; ascending aorta, 0.8 cm; the thoracic aorta just below the ductus, 1.5 cm.

The lower edge of the liver lay 2 cm. below the costal margin. It weighed 80 grams.

CASE 4 (K.S.)—*Extreme aortic stenosis with hypoplasia of the left heart and aortic arch; dilated pulmonary artery; hypertrophy and dilatation of right atrium and right ventricle; functionally closed foramen ovale; patent ductus arteriosus; accessory leaflet of tricuspid valve; marked congestion of lungs and abdominal viscera.*

This white male infant, aged 2 days at death, was delivered spontaneously at term following an uneventful pregnancy. The birth weight was 3,200 grams. Two siblings were living and well. The mother was 24 years old and the father 29. During the four days prior to delivery, the mother experienced intermittent vaginal bleeding. The infant was cyanotic at birth and required resuscitation before spontaneous respirations commenced. His color improved only moderately with oxygen, and his cyanosis never cleared completely. He became progessively more dyspneic. He was first seen at The Children's Hospital of Philadelphia at the age of 19 hours. At this time he appeared in acute respiratory distress with a rate of 80 per minute, flaring of the alae nasae, and subcostal retractions. His skin had a dusky, grayish-blue color. The heart sounds were strong and the cardiac rate was 160 per minute. No murmurs were audible. P_2 was not reduplicated. There was some cardiac enlargement to percussion. The blood pressure could not be obtained, and the femoral pulses were not palpable. The liver was firm, smooth, and glossly enlarged, being palpable at the level of the umbilicus on the right. Dyspnea, hepatomegaly, and cyanosis became progressively more marked despite the use of oxygen, morphine sulfate, and digitalis. The patient expired 26 hours after admission.

Roentgen Findings (Fig. 4).—The heart was enlarged and globular in

shape. The left border extended to the left thoracic wall. The contour suggested hypertrophy of the right ventricle. *Electrocardiogram:* There was marked right axis deviation. The T waves were inverted in Lead I. The S waves were prominent in Leads 1 and 2.

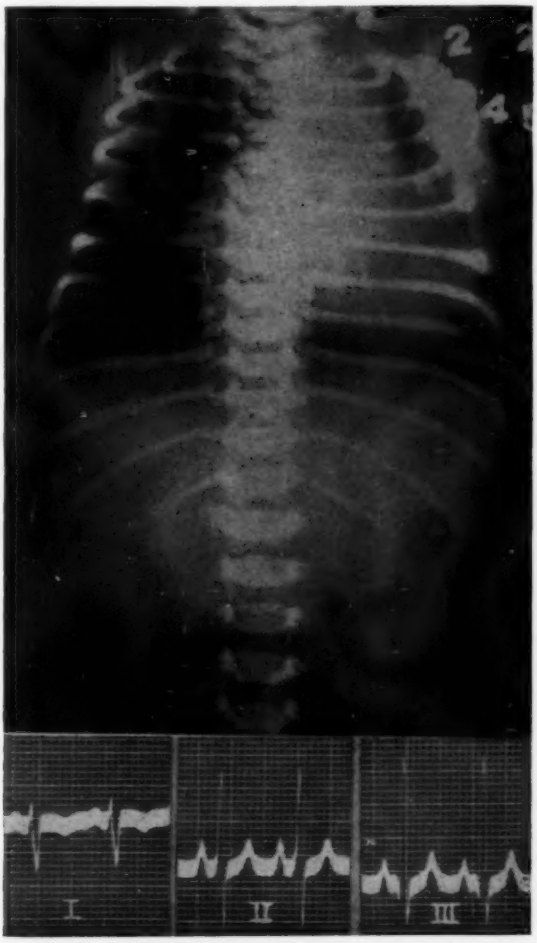

Fig. 4 (Case 4).—The roentgenogram shows definite cardiac enlargement with fulness of the pulmonary segment. The electrocardiogram shows right axis deviation with inversion of T waves in Lead I and high P waves in Lead II.

At necropsy, the heart weighed 44 grams. It presented the general appearance described in the previous cases with predominant enlargement of the right heart and pulmonary artery associated with hypoplasia of the left heart and aortic arch. The right ventricle formed the apex of the heart. In addition to the three normal cusps of the tricuspid valve, a tiny leaflet was attached to the cristal papillary muscle. The left atrial appendage was the

same size as the right, but the left atrium was much smaller. The diminutive mitral valve was provided with two tiny cusps of normal configuration. A diminutive left ventricle was situated within the superior posterior portion of the ventricular mass. A markedly stenotic aortic orifice surrounded with nodular excrescences barely permitted the passage of a hairpin prong. The foramen ovale was anatomically open to the passage of a sound, but was functionally closed. The following measurements were noted: circumference of tricuspid valve 5.5 cm.; pulmonary valve 2.7 cm.; mitral valve 1.2 cm.; diameter of pulmonary artery 1.8 cm.; ascending aorta 0.5 cm.; isthmus of aorta 0.3 cm.; thoracic aorta distal to entrance of ductus 1.2 cm. The ductus arteriosus measured 0.4 x 0.8 cm.

The liver weighed 55 grams. Its lower border lay 4 cm. below the costal margin.

DISCUSSION

The cases described above have in common two basic features: (1) aortic valvular atresia and (2) hypoplasia of the left heart. Several of the associated anomalies, such as patent ductus arteriosus and foramen ovale, hypoplasia of the aortic arch and enormous hypertrophy and dilatation of the right heart are considered secondary or compensating by most observers. In the four cases included in this report, it was not difficult to decide that the primary lesion was the aortic one, since in each instance the mitral orifice was rudimentary but anatomically intact, that is, it consisted of two small mobile valve leaflets with diminutive chordae tendineae attached to the free edges of the cusps. Thus the mitral valves were essentially normal except for their small size. Examination of the aortic valve areas in our patients revealed complete absence of the valvular structures at the junction of the left ventricle and aortic arch in two patients and essentially complete atresia with fusion of the three valve cusps in the other two. The structures proximal and distal to the closed aortic valve such as the left ventricle, mitral valve, and aortic arch were underdeveloped and undersized presumably because they had never had an opportunity to function normally.

In spite of the hypoplasia of the left heart, in the eighteen cases in the literature in which heart size was mentioned, sixteen were stated to be above normal in size. The hearts in our four patients were all enlarged. In only one reported case[29] was a right aortic arch associated with this anomaly.

The foramen ovale was completely closed in one infant in our series. In the other three infants the opening was small and so directed as to permit the passage of blood only from right to left. All four infants showed chronic passive congestion of the viscera as determined by microscopic examination. The alveolar capillaries particularly were markedly dilated. The alveolar spaces in the patient in Case 4 showed many phagocytes containing yellowish-brown pigment. In the infant in Case 1 small numbers of monocytes were present in the alveolar spaces.

In practically all reported cases the coronary arteries arose in the normal manner. Since little if any blood is expelled through the aortic orifice, these vessels are not filled in the usual fashion. As suggested by Roberts,[22] blood reaches the coronary bed from the following sources: (1) retrograde flow from the ductus arteriosus, (2) from the lumen of the heart through the Thebesian veins, (3) from the lumen of the right atrium through the dilated coronary sinus and its tributaries as suggested by the congested

coronary veins, (4) from the extra cardiac anastomoses between the coronary system and the blood vessels in the fat and other tissues at the base of the heart.

In each of our four cases the subject was a male. Twenty-seven of the cases accepted from the literature mentioned the infant's sex and eighteen of these were also males. The pregnancy histories of our four patients revealed nothing consistently unusual. The birth weights of these infants were variable. Cyanosis and dyspnea were prominent clinical signs in some stage in each patient's course. What is perhaps more surprising is the frequent history of a period of absence of symptoms prior to a sudden onset of cyanosis and respiratory distress. It is difficult to imagine how oxygenated blood could have passed through the foramen oxale in sufficient amount to prevent the appearance of cyanosis and respiratory distress from the moment of birth. Precordial murmurs were not uniformly audible but when present were systolic in time and best heard to the left of the sternum. A low or unobtainable blood pressure and weak or unobtainable pulses in both arms and legs might also be anticipated with this malformation.

Roentgenographic and fluoroscopic examination in three of our cases confirmed the presence of massive cardiac enlargement which in two instances almost obscured the lung fields (Fig. 2), associated with fulness of the pulmonary segment. In the right anterior oblique view, the filling of the retrosternal space by the cardiac shadow suggested a right ventricular hypertrophy. The only two published roentgenograms,[8, 33] illustrate similar findings. Taussig[28] has described similar fluoroscopic findings due to enormous enlargement of the right ventricle with distention of the pulmonary artery, the right atrium, and superior vena cava. In one of our cases, however (Fig. 3), the roentgenograms taken at birth and again at 10 days of life failed to demonstrate any marked degree of cardiac enlargement up to that time. At necropsy eight days later, enlargement of the right ventricle was found. Thus, this represents an exception to the rule that demonstrable cardiac enlargement is usually present at the time of birth.

In only one previously reported case was an electrocardiogram obtained. Right axis deviation was noted. Two of our patients showed right axis deviation in the electrocardiogram. A third tracing taken shortly before death showed left bundle branch block. Right axis deviation would be the expected finding in view of the predominant enlargement of the right side of the heart. However, Soloff[25] has reported an instance in which left axis deviation was recorded in the limb leads of a case with characteristic findings of hypogenesis of the left ventricular system associated with both mitral and aortic atresia. In the records of the Department of Cardiology of The Children's Hospital of Philadelphia, there is a case of mitral atresia with left-sided hypoplasia showing left axis deviation in the limb leads of the electrocardiogram.

As reported in the literature, the survival time of infants with this combination of anomalies has varied from one day to four months. In our series of four patients, none lived longer than eighteen days. Of the thirty-four patients summarized in Table I, twenty-four died within the first week of life,

three died within the second week, and two others failed to survive the third week. One infant died on the twenty-fifth day after birth, while two others were reported to have survived for considerably longer periods, one for fifteen weeks and the other for four months. The age of death was not mentioned in two cases.

General agreement exists concerning the abnormal hemodynamics in this type of malformed heart. The right atrium is filled in the usual fashion by venous blood from the superior and inferior venae cavae. In fetal life little if any blood is propelled through the foramen ovale into the left side of the heart as evidenced by the minute size of the left chambers and by the frequent finding of a bloodless left ventricle. Since the right ventricle provides the only effective pumping chamber of the heart it becomes greatly hypertrophied. Blood from the right ventricle courses not only past the pulmonary valve into the pulmonary artery but also through the patent ductus into the descending aorta. In the aorta the blood may proceed in one of two directions, either caudad through the descending aorta to supply the systemic circulation, or cephalad in retrograde fashion into the hypoplastic aortic arch to supply the coronary arteries and vessels to the head and neck. This abnormal circulatory arrangement results in right ventricular hypertrophy, even in fetal life, but is adequate to maintain fetal circulation without difficulty. Influences which operate favorably during fetal life and terminate at birth are: (1) the lowered oxygen requirement of fetal tissues, (2) the small volume of fetal pulmonary circulation, and (3) the unhampered source of oxygen supply from the maternal circulation.

After birth, the pulmonary veins bring oxygenated blood to the left atrium. Because of the impediment provided by the hypoplastic left ventricle with its blind aortic orifice, the blood arriving from the lungs must take an anomalous route. Life can be maintained only if this oxygenated blood passes through the foramen ovale into the right atrium and if the ductus arteriosus remains patent so as to provide a pathway into the aorta. The size of the foramen ovale and its functional capacity are important determinants of the length of survival of these patients.[22] In none of the four infants reported in this paper was the patency of the foramen ovale sufficiently great to permit the passage of an adequate amount of oxygenated blood into the right atrium.

The two physiopathologic abnormalities to which these patients finally succumb are congestive heart failure and generalized severe anoxemia. That congestive failure has already begun during fetal life is evidenced by the frequent finding of marked right ventricular hypertrophy, engorgement of the venous system, and enlargement of the liver at birth. Progressive anoxemia develops as a result of various factors. The requirement of tissues for oxygen increases in postnatal life. The effects of anoxia on the myocardium may cause additional embarrassment when that muscle is striving to perform an increased amount of work. A major handicap is introduced by the gradual building up of left intra-atrial pressure due to the introduction of an increased amount of blood from the expanded pulmonary circulation. With the rise of pressure in the left atrium,

the valve of the foramen ovale is compressed against the interatrial septum so as to close the orifice and prevent the transmission of blood into the right atrium.[12] Unless a large interatrial defect is present, the postnatal increase in pressure in the left atrium thus effectively cuts off the only source of oxygenated blood to the systemic circulation. Even in the presence of an interatrial defect of adequate size there is the possibility of closure of the patent ductus. Such closure of the foramen ovale or ductus arteriosus may explain the sudden onset of critical symptoms and rapid demise after a brief benign course.

From the foregoing discussion, there appears to be little hope for success in surgical intervention, even if the enormous technical difficulties could be surmounted. The benefit to be derived from an aortic valvulotomy would be offset by the hypoplastic, noncontractile state of the left ventricle. Effective aid could be provided by enlarging the interatrial defect, thus permitting oxygenated blood eventually to reach the systemic circulation. Early diagnosis, prior to the onset of frank right-sided congestive failure and irreversible changes due to anoxemia, would be an absolute prerequisite to any surgical approach. With the help of careful fluoroscopic examination, a clinical diagnosis is possible in some cases. Recent advances in the technique of angiocardiography might possibly permit confirmation of the diagnosis in the relatively few infants who live long enough to make such diagnostic procedures possible. However, the distortion of the hemodynamics is so profound in this condition that little permanent benefit can be anticipated from surgery.

SUMMARY

1. Four cases of congenital aortic atresia with hypoplasia of the left heart are presented together with a review of the literature. Cases with associated deformity or absence of the mitral valve are excluded.

2. The etiology, clinical diagnosis, and pathologic physiology of this malformation are briefly discussed.

3. The possibility of benefit from surgical intervention in this variety of congenital heart disease is evaluated. The production of an interatrial defect would be the only helpful surgical procedure, but in view of the profound distortion of the hemodynamics little permanent benefit can be anticipated even if the enormous technical difficulties could be surmounted.

We are indebted to Dr. Irving J. Wolman for placing at our disposal the pathologic material in these cases.

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Addendum

Since submitting this paper for publication, one of the authors (R. A.) has had the opportunity to observe two additional male infants who died in the neonatal period with congestive failure evidenced by the presence of dyspnea, progressive enlargement of the liver, and moderate cyanosis. Both infants seemed normal for several days following birth. Neither demonstrated any marked degree of cardiac enlargement in the roentgenogram. The electrocardiogram in both cases showed right axis deviation. Death occurred on the ninth and the tenth day, respectively. Necropsy revealed in each infant complete atresia or absence of the aortic valve in association with hypoplasia of the left heart and a normal but diminutive mitral orifice.

Two additional instances of this malformation were also discovered in the literature (Lev, M., and Killian, S. T.: Hypoplasia of the Aorta Without Transposition With Electrocardiographic and Histopathologic Studies of the Conduction System. [Case 2], Am. Heart J. **24**: 794, 1942. McNearney, J. C.: Congenital Atresia of the Aortic Orifice, Yale J. Biol. Med. **9**: 229, 1936), thus making a total of thirty-eight reported cases.

Case Reports

THE SHWARTZMAN PHENOMENON COMPLICATING ACUTE MENINGOCOCCEMIA WITH MENINGITIS

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SHWARTZMAN,[1] in 1928, described a phenomenon of local tissue reactivity. In his excellent monograph, Shwartzman[2] describes the phenomenon of local skin reactivity to various microorganisms and its immunological, pathological, and clinical significance. The basic experiments consist of a preparatory intradermal injection of *Bacillus typhosus* culture filtrate in a rabbit, followed twenty-four hours later by a provocative intravenous injection of the same filtrate. A severe hemorrhagic necrosis occurs at the prepared skin site four hours following the intravenous injection. Grossly, the skin site is dark blue, edematous, and has a red periphery. Microscopically, there is disruption of the venules, extensive hemorrhage, thrombosis, and necrobiosis of all the cells. The reaction traverses through the superficial skin layers and the abdominal wall of the rabbits. Repeated skin injections, at twenty-four-hour intervals, of the bacterial culture filtrate fail to produce the hemorrhagic, necrotic reaction. The second or provocative injection must be given intravenously. Shwartzman also elicited the phenomenon by provocative intravenous injections of bacterial filtrates. A generalized Shwartzman reaction, consisting principally of a bilateral cortical renal necrosis, is elicited by injection of the active principles, intravenously, twenty-four hours apart. Among the bacteria producing active principles of high potency for the phenomenon of local tissue reactivity are: meningococcus, *B. typhosus, B. paratyphosus, B. coli, B. friedländer, B. dysenteriae, B. prodigiosus, B. lepisepticus, B. pestis, Hemophilus influenzae, H. pertussis,* and *Vibrio cholerae.*

Black-Schaffer, Hiebert, and Kerby[3] experimentally confirmed the fact that twice-washed living or dead meningococci possess potent preparatory and provocatory substances which can produce the local Shwartzman phenomenon. These workers hypothesize that in meningococcemia in man, each cutaneous lesion is a miniature Shwartzman reaction. Frequently, prior to the clinical onset of the disease, there is a focal infection of the upper respiratory tract, which feeds meningococci into the blood stream. The organisms and their products deposit in the skin and prepare it. The patient's reactivity and the meningococcus strain are the factors affecting the length of time for the preparation of the skin. The purpuric lesions result from the provocatory effect of the bacteriemia. The extent of the cutaneous lesions is again dependent upon the patient's reactivity and the virulence of the meningococcus strain. The successive crops of petechiae are due to the provocatory effect of foci that are established later in the course of the bacteriemia.

In discussing the clinical implications of the Shwartzman phenomenon, Black-Schaffer[4] emphasizes that some patients with very fulminating meningococcemia succumb in spite of antibiotic therapy. He suggests that the development of an antiserum directed not only against the meningococci, but

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against the Shwartzman toxin as well, would help eliminate fatalities due to Shwartzman-potent bacteria.

The following case report is that of a 7-month-old infant who developed a severe Shwartzman reaction early in the course of meningococcemia.

CASE REPORT

M. H., a 7-month-old white male, was admitted to the Beth-El Hospital on Dec. 4, 1949, with the chief complaint of "high fever and blood spots under the skin." The previous day the infant was seen in the office of one of us for a routine check-up, and at that time was perfectly well. He received his first immunization injection of diphtheria, pertussis, tetanus combined vaccine (0.5 c.c.). Six hours later the infant's temperature rose to 104° F., rectally, and he was given aspirin. He continued to run fever between 103° and 104° F. An hour before admission, the mother noticed widespread "spots of blood under the skin." The family and past history are noncontributory.

Physical examination on admission revealed a well-nourished 7-month-old male infant, weighing 21 pounds, 5 ounces, who appeared acutely ill but was alert. The rectal temperature was 100.8° F., the pulse rate 140 per minute, respiratory rate 32 per minute. The blood pressure was 80/40. A generalized petechial and purpuric eruption was present over the face, trunk, and extremities. The skin over the buttocks and thighs was one coalescent ecchymotic area. Both eardrums were red. The pharynx and nose were inflamed. No clinical signs referable to the central nervous system were present.

A complete blood count, blood culture, nose and throat culture, urinalysis, and urine culture were done. A direct smear from the purpuric areas was made. The infant was placed in an oxygen hood, and penicillin 100,000 units intramuscularly every three hours, sulfadiazine 1.0 Gm. initially and 0.4 Gm. every four hours orally, and aureomycin 125 mg. orally were given. Vitamin K, 4.8 mg., was given intramuscularly. Fluids were forced. The petechial smear revealed many gram-negative intracellular and extracellular diplococci. The admission hemogram was: red blood count 3.58 million per cubic millimeter, hemoglobin 55 per cent, white blood count 7,400 per cubic millimeter, with a differential count of 35 per cent staff cells, 44 per cent segmented cells, 19 per cent lymphocytes, and 2 per cent monocytes, and platelets 290,000 per cubic millimeter. Urinalysis was negative except for a faint trace of albumin.

The infant appeared to be responding well to therapy when suddenly, six hours after admission, a generalized convulsion occurred. The rectal temperature was 101° F. The convulsion was terminated with the administration of phenobarbital sodium intramuscularly and ether by open drop. A spinal tap was done and revealed cloudy fluid under increased pressure. There were 6,000 white blood cells per cubic millimeter, predominantly polynuclears. A gram stain of the sediment revealed gram-negative diplococci. A cut-down was performed on the right saphenous vein and parenteral fluids administered. Sodium sulfadiazine, 1.0 Gm. initially, and 0.33 Gm. every four hours, was started, intravenously. Penicillin dosage was increased to 1 million units every three hours. Ten cubic centimeters of adrenal cortical extract was given intravenously. A rectal tube was inserted to help relieve the abdominal distention.

Eighteen hours after admission, it was evident that the response to therapy was excellent. The rectal temperature was 100° F. The infant was alert, taking fluids by mouth avariciously, and urinating well. There were no meningeal signs. There was a marked generalized purpura which was very prominent over the buttocks and thighs and the possibility of a slough was suspected (Fig. 1). The tip of the spleen was palpable, and a systolic murmur was heard at the apex. An electrocardiogram at this time, however, was normal except for a sinus

Fig. 1.

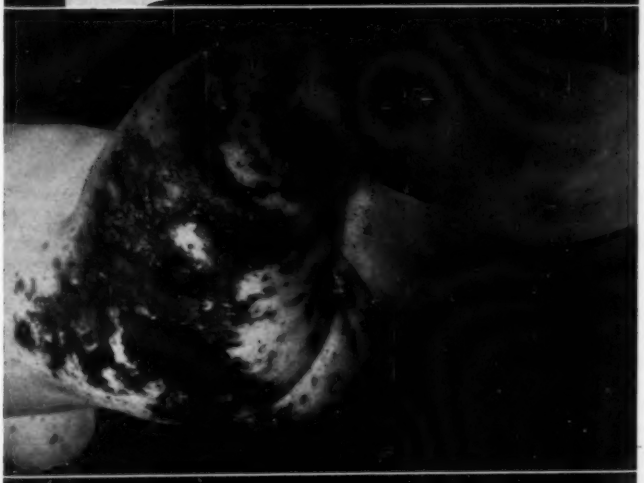

Fig. 2.

Fig. 3.

Fig. 1.—The marked, confluent purpura that occurred early over the buttocks and upper thighs is readily seen.

Fig. 2.—The areas of purpura seen in Fig. 1 now exhibit necrotic changes and are shown having an escharlike appearance, with beginning undermining slough at the periphery.

Fig. 3.—The whole area has sloughed, and granulations with epithelization are seen.

tachycardia. Intravenous fluids were discontinued. Penicillin dosage was reduced to 100,000 units intramuscularly every three hours, aureomycin therapy was stopped, and sulfadiazine was given by mouth.

On the third hospital day, the temperature began to spike between 100° and 103° F., but the infant was alert and the only new physical findings were erosion of skin and blister formation in certain of the ecchymotic areas, especially over the buttocks. The temperature rise was ascribeable to the start of necrosis and gangrene of the skin and absorption of blood from the extensive purpura.

The next day the infant's clinical condition appeared good but the fever persisted. Aureomycin 100 mg. every four hours by mouth was instituted. A repeated spinal tap revealed fluid that was faintly cloudy, with 220 white blood cells, 75 per cent polynuclear. The spinal fluid culture was negative. It was apparent that the primary therapeutic problem at this time was the care of the infant's skin. The patient was placed on his abdomen and covered with a heat cradle that supported sterile bed linens. For the secondary anemia and the skin condition, blood transfusions of 125 c.c. each were given for the next three days. The temperature continued to range between 100° and 102.4° F. until the eighth hospital day, when the infant became afebrile. Meanwhile the purpuric spots were fading except for an area 1.5 cm. in circumference on the right cheek, and the buttocks and upper posterior region of the thighs which had a black eschar that started sloughing along the periphery (Fig. 2). By the thirteenth day, the lesion on the cheek had sloughed, leaving a clean, deep, granulating ulcer. Sulfadiazine and aureomycin therapy was stopped but penicillin was continued. On the sixteenth hospital day, the infant had a temperature of 100° to 101.6° F. The child was well except for the skin, which showed sloughing of the buttocks with deep ulcers, some of which were superficially infected. Small doses of ultraviolet irradiation were started and aureomycin therapy given. On the twenty-first day, the infant became afebrile and remained so for the remainder of his hospital stay. By the twenty-fourth day, the necrotic skin over the buttocks and thighs had completely sloughed and relatively clean granulations were forming.

On the thirty-fourth hospital day, the infant's general condition was good and the buttocks were epithelializing from the periphery. Therapy was limited to aureomycin, ultraviolet irradiation, and supportive therapy with blood and irradiated plasma transfusions. At this stage, surgery did not appear to be indicated, although the possibility that skin grafting might become necessary was considered. On the forty-seventh hospital day, the patient was discharged from the hospital. At this time his buttocks were healing so well that no further treatment was indicated (Fig. 3).

Specimens of blood taken from the patient on Dec. 31, 1949, and Jan. 13, 1950, revealed that his serum was agglutinated with type specific monovalent meningococcic antigen of Group 1-3 in a titer of 1:1,600.

COMMENT

De Fuccio and Dresner[5] recently reported a case of meningococcemia with meningococcal meningitis in a 7-year-old Negro male, that was complicated by gangrene of the lower extremities, necessitating amputation of the lower third of both legs. These authors do not mention the possible role of the Shwartzman phenomenon in the etiology of the complication of gangrene in their case.

Hill and Kinney,[6] in a study of twenty-five autopsied cases, presented the clinical and pathological features of the skin lesions in acute meningococcemia. Most of their cases presented varied cutaneous lesions, including erythematous macules, papules, nodules, vesicles, petechiae, and purpura. Macules over the trunk and lower extremi-

ties appeared first. Many petechiae coalesced to form larger purpuric lesions, some of which even enveloped an entire segment of the body. The extremities were the commonest site for the skin lesions but other areas subject to pressure and friction were frequently involved. Petechiae were commonest over the joints while purpura showed a predilection for the extremities and back. The skin lesions generally appeared twelve to thirty-six hours after the institution of chemotherapy, the maculopapular lesions usually faded, but hemorrhagic lesions were not affected. Two surviving patients presented necrosis and sloughing of the purpuric lesions, with complicating gangrene of the extremities. One of these patients required amputation of the toes, and both underwent a long period of hospitalization.

In discussing the pathology of the cutaneous lesions in acute meningococcemia, Hill and Kinney[6] emphasize that the fundamental lesion is one of diffuse vascular damage featured by a dilatation and engorgement of the blood vessels. Smaller blood vessels and capillaries have a swelling of the endothelial cells. Platelet thrombi are present in many blood vessels. The authors feel that the presence of the meningococci causes the vascular damage. The organisms localize in the endothelium, resulting in endothelial changes and inflammation of the vessel walls, with subsequent necrosis and thrombosis. The hemorrhagic lesions are caused by the extravasation of red blood cells from the damaged vessels. Vascular thrombi account for the late complication of gangrene. Apparently the control of the bacteriemia did not prevent the occurrence of gangrene in the authors' two cited cases. Dehydration, loss of vascular tone, and stasis promote the continued propagation of the thrombi, and account for the eventual gangrene. The authors feel that as modern chemotherapy helps more patients survive the initial bacteriemia, the skin complications will become more apparent.

The Waterhouse-Friderichsen syndrome, which is at times a dramatic complication of meningococcemia, is apparently not part of the Shwartzman phenomenon. Black-Schaffer, Hiebert, and Kerby[3] point out that since only a small number of patients with purpuric meningococcemia develop adrenal necrosis that purpuric meningococcemia is not synonymous with the Waterhouse-Friderichsen syndrome. Experimentally, a single intravenous inoculation of potent bacterial filtrate can produce adrenal necrosis. However, the Schwartzman phenomenon may be elicited only by first preparing the site and then provoking the response by an intravenous inoculation. Therefore, they feel that the adrenal necrosis may not be considered part of the Shwartzman phenomenon. The adrenal lesions are a by-product of a general toxemia and not a result of the Shwartzman phenomenon.

The excellent pathological descriptions of Hill and Kinney[6] bear a striking resemblance to the gross and microscopic descriptions of the Shwartzman phenomenon. However, Hill and Kinney[6] do not consider, nor mention this similarity. We feel that the work of Shwartzman and Black-Schaffer and his co-workers represents strong experimental evidence for the incrimination of the Shwartzman phenomenon as an underlying cause for the complicating cutaneous lesions in acute meningococcemia. Therefore, we consider our patient as a case of acute meningococcemia with meningitis, complicated by the appearance of the Shwartzman phenomenon. "In terms of the phenomenon the obvious mechanism is as follows: the toxic products of meningococci lodged in the capillaries of the skin may serve as the preparatory factor, while the meningococci or their toxic products circulating in the blood stream may serve as the provocative factor."[7]

SUMMARY

1. A case of acute meningococcemia with meningitis complicated by the

Shwartzman phenomenon in a 7-month-old white male infant is reported.

2. The Shwartzman phenomenon is briefly described and the etiological and pathological aspects of the cutaneous complications of acute meningococcemia are reviewed.

3. The role of the Shwartzman phenomenon in causing cutaneous lesions in acute meningococcemia is emphasized.

We wish to express our deep gratitude to Dr. Bela Schick, of the Department of Pediatrics of the Beth-El Hospital, for his encouragement and assistance in the preparation of this paper. We wish also to thank Dr. Gregory Shwartzman for reviewing this paper and for pointing out to us the mechanism of the Shwartzman phenomenon in the case we have reported.

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HEMOPHILUS INFLUENZAE PYARTHROSIS AND MENINGITIS TREATED WITH AUREOMYCIN

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WEAVER and Sherwood[5] summarized twenty-two cases of *Hemophilus influenzae* pyarthrosis reported in the literature and added two of their own. Eleven of the twenty-four patients had meningitis with pyarthrosis. Five of these patients had multiple joint involvement, but in no case was it symmetrical. All of the patients with meningitis died. Thirteen cases of pyarthrosis without meningitis were reported. In this group, two had asymmetrical multiple joint involvement. There was only one death due to erysipelas after the joint infection had healed in those patients without meningitis. On recovery, most of the patients had good function in the involved joints. All cases occurred between the ages of 4 and 20 months except one which occurred in a 59-year-old person. Weaver and Sherwood did not include nine cases reported by Peterson[3] in their review of the literature because they could not find ample evidence to support the diagnosis.

The first reported case of pyarthrosis caused by *H. influenzae* was by Slawyk[4] in 1899. Pyarthrosis can be caused by various bacteria gaining entrance to the joint cavity. *H. influenzae* is one of the less common organisms causing this disease, the most common being staphylococcus, pneumococcus, streptococcus, gonococcus, and meningococcus. The reported successful use of aureomycin in the treatment of *H. influenzae*[1, 2] prompted the use of aureomycin in this patient.

CASE SUMMARY

An 8-month-old Negro male infant was admitted to the University Hospital pediatric service on Nov. 28, 1949, with the chief complaint of progressive swelling of both elbows over a period of six weeks. The swelling, which had been minimal at the onset, increased intermittently and had been associated with pain for five weeks. Fever was also present at the onset of the illness, but local heat was never noted by the mother. There had been no anorexia, but the infant had lost about five pounds in six weeks. A mild chest cold with cough had been present intermittently for four months. The infant had been followed by his family physician for two weeks prior to admission and had received three injections of procaine penicillin, the last injection two days before admission.

The past history revealed a full-term, uncomplicated pregnancy with a normal delivery. The birth weight was 9 pounds, and he was breast fed for one month. He had gained steadily on an adequate diet and Oleum Percomorphum had been given daily until one month before admission. Orange juice was started at one month and he had received it daily. Immunizations were in progress.

The family history revealed both of the parents and nine siblings to be in good health. The mother had had three stillbirths, the etiology unknown.

The admission physical examination revealed a well-developed and well-nourished 8-month-old Negro male who appeared well except for acute pain when his arms were examined. The temperature was 101.4° F. rectally, the pulse 130 per minute, and the respirations 28 per minute. The infant weighed 18 pounds, 3 ounces. He was well hydrated. The skin was clear. The anterior fontanel was almost entirely closed. The eyes were

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negative except for pale conjunctivae. Slight nasal congestion was present. The neck was flexible. There was a short rough systolic murmur in the second and third intercostal spaces to the left of the sternum. The abdomen was negative. Positive findings in the extremities were limited to both elbows. They were markedly swollen and tense, warm, acutely tender, held in semiflexion, and the child resisted all examination of them. There was fluctuancy on the lateral aspect of the left elbow.

The admission laboratory work revealed hemoglobin of 7 Gm. (48 per cent), red blood cell count 5,450,000, white blood cell count 17,350 with a predominance of polymorphonuclear cells. The urinalysis was normal. The admission roentgenograms revealed a normal chest, normal skull, and arthritis of each elbow. Fig. 1 represents the right elbow at the time of admission. Similar findings were present in the left elbow.

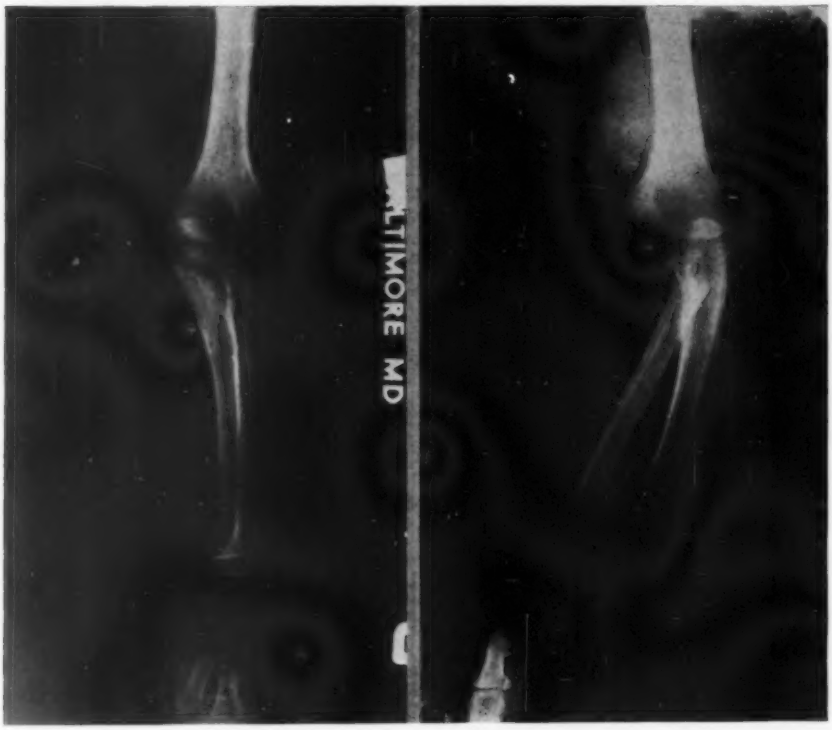

Fig. 1.—Roentgen examination of the right elbow in anterior and lateral views on Nov. 28, 1949, shows partial destruction of the proximal metaphysis of the radius. A large amount of fluid is present in the joint, and there is questionable periosteal proliferation along the shaft. The same picture was present in the left elbow.

An admission diagnosis of pyarthrosis and upper respiratory infection was made and the infant was given 300,000 units intramuscularly of Crysticillin on admission and daily thereafter. The hospital course and pertinent laboratory data are summarized on Chart I.

On the second hospital day, both elbow joints were decidedly fluctuant

and needle aspirations were performed with the removal of 20 c.c. of bloody, purulent material from each joint space. On the fourth hospital day, a culture of this material revealed *H. influenzae*, type B. Crysticillin was discontinued and the child was placed on aureomycin, 100 mg. every four hours orally. On the same day, the child developed nuchal rigidity, lateral nystagmus, and irritability. A lumbar puncture was done, and the spinal fluid contained 820 white blood cells with 40 per cent polymorphonuclear cells and 60 per cent lymphocytes. The spinal fluid sugar was 8 mg. per cent. The culture was positive for *H. influenzae*, type B. On the fourth hospital day, both elbow joints were aspirated for the second time and 15 c.c. of purulent material was removed from each joint space. This material was again positive for *H. influenzae*. On the fifth hospital day, the temperature dropped to normal for the first time but the meningeal signs persisted. The joints did not swell as rapidly as they had previously. Frequent lumbar punctures revealed the persistence of increased white blood cells with a reversal of the original polymorphonuclear lymphocyte ratio. The spinal fluid sugar determinations remained low, and the cultures continued to be positive for *H. influenzae*. A few râles developed in the right upper chest, and on the eighth hospital day, a chest x-ray revealed a bilateral pneumonitis.

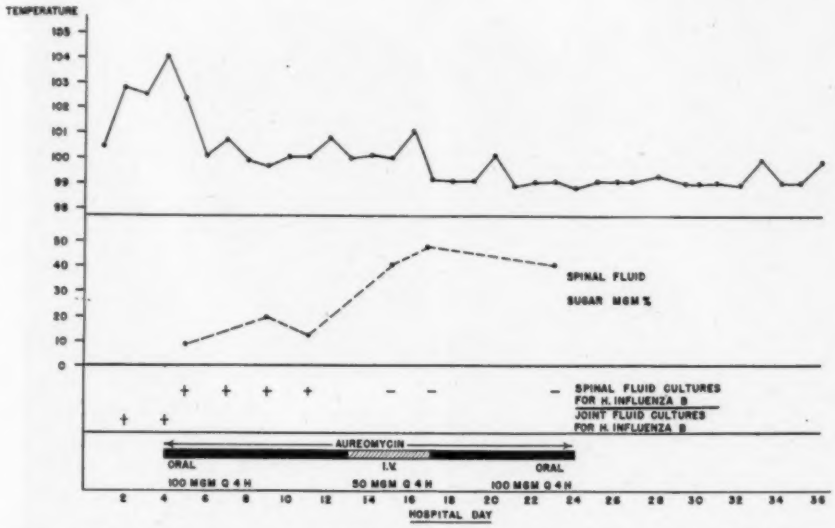

Chart I.—Hospital course of infant with *H. influenzae* pyarthrosis and meningitis treated with aureomycin.

A low-grade fever persisted, and the aureomycin was administered intravenously rather than orally for a period of eighty hours beginning on the thirteenth hospital day. A dose of 50 mg. every four hours was given, and during this period the child symptomatically improved. He was less rigid and irritable, and the swelling of his elbows was minimal although there was still much pain present. The spinal fluid culture was negative for the first time on the fifteenth hospital day.

On the seventeenth hospital day, oral aureomycin was resumed with a dose of 100 mg. every four hours.

During the remainder of his hospital course the temperature remained normal except for rare, slight elevations. Symptoms of meningeal irritation cleared slowly, and he became more relaxed although it was felt that he had sustained a moderate amount of cerebral damage. The swelling of his elbows resolved, but he held these joints in semiflexion and did not use his arms voluntarily. Great pain persisted. Orthopedic consultation advised against physiotherapy or passive motion. Repeated blood cultures were negative. Old tuberculin skin test 1:10,000 and 1:1,000 dilution was negative as was the blood serology. The infant was discharged on the fiftieth hospital day.

The patient has been seen in the Out-Patient Department on three occasions since discharge, the last visit occurring at the age of 13 months (five months after his discharge from the hospital). At that time his nutritional status was very good. He had remained afebrile, and there was no evidence of recurrence of the infectious process. His development was retarded, and although he was able to assume a sitting position, he was not able to sit alone for any length of time or pull himself up. Neurologic examination was normal except for a possible impairment in hearing. He had good use of both arms. The left elbow joint was entirely normal but there was some loss of motion in the right elbow joint.

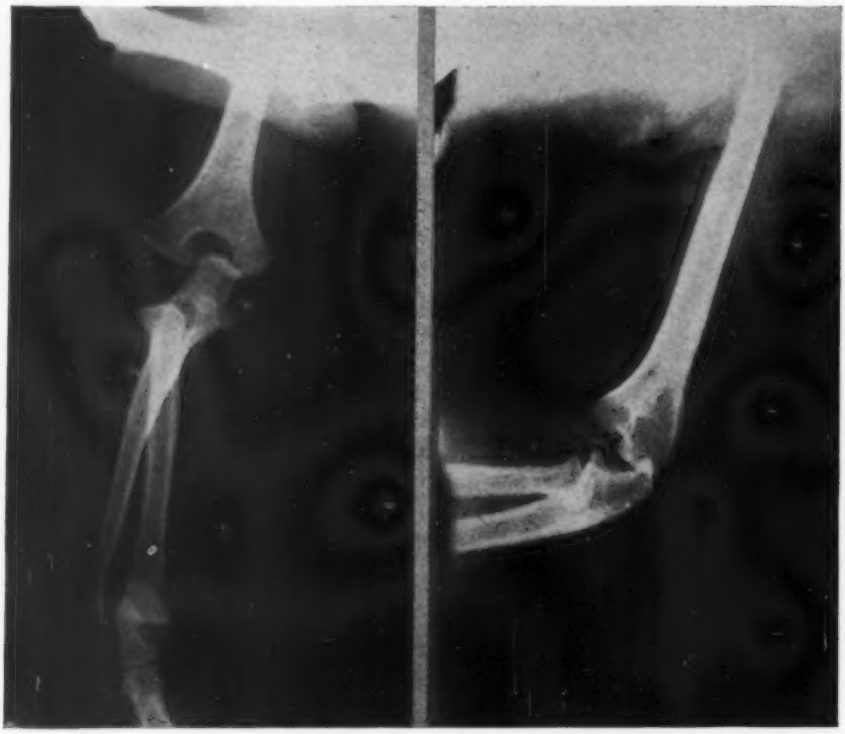

Fig. 2.—Roentgen examination of the right elbow in anterior and lateral views on June 19, 1950, shows the radial head and articular surfaces of the olecranon process to be quite irregular due to new bone formation, but there is no evidence of bony destruction, and the joint space is of normal width. The same picture was present in the left elbow.

He was unable to fully extend the right forearm and could adduct it only to 90 degrees. Fig. 2 representing the roentgenograms of the right elbow taken on June 19, 1950, shows healed infectious arthritis.

DISCUSSION

None of the previously reported cases of *H. influenzae* pyarthrosis and meningitis were treated with any chemotherapeutic agent. The mortality in these cases was 100 per cent. The patient reported here, treated with aureomycin, survived. The child has residual brain damage from the infection but the exact extent is unknown as he is still showing some improvement. Chandler[1] and Drake[2] have obtained satisfactory results in the treatment of *H. influenzae* meningitis with aureomycin.

The optimal dosage of aureomycin is as yet not determined. Using a larger dose initially or starting with intravenous aureomycin might have given a more prompt response in this patient. It is evident that *H. influenzae* responds to aureomycin; however, the best chemotherapeutic agent or combination of agents remains to be determined.

SUMMARY

A case of *H. influenzae* causing pyarthrosis and meningitis treated with aureomycin is described.

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SUPRASELLAR (RATHKE'S POUCH) CYST

Report of Unusual Case Simulating Successively Rheumatic Fever, Encephalitis, and Brain-Stem Tumor; Prolonged Postoperative Recovery and Development of Pubertas Precox*

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John M. Meredith, M.D.,* Richmond, Va.

INTRODUCTION

TUMORS arising from the remnants of the embryonic craniopharyngeal pouch of Rathke are fairly common, comprising about 4½ per cent[1] of intracranial tumors occurring at all ages and a considerably greater portion of the tumors of childhood, the peak incidence occurring at about 12 to 13 years of age.[2] A case of this particular lesion which we have observed at intervals for more than five and one-half years has several features of unusual diagnostic, therapeutic, and endocrine interest.

First, the early clinical course, when seen in the Pediatric Clinic, strongly suggested rheumatic fever on the basis of a febrile course, leucocytosis, a painful elbow joint, anorexia, weight loss, choreiform movements, and a P-R interval in the electrocardiogram of 0.16 second, which was regarded as somewhat prolonged.

Later, because of progression of the neurological picture and the finding of spinal fluid abnormalities, neurosurgical consultation was requested. It was the consultant's first opinion that the syndrome of febrile illness, fixed dilated pupils, choreiform and myoclonic movements, bilateral spasticity of the extremities and positive Babinski signs, elevated spinal fluid sugar content, and normal optic fundi with, apparently, normal cerebrospinal fluid pressure, indicated a virus encephalitis. When papilledema subsequently developed, we modified our impression to include "brain-stem tumor," although the clinical course continued predominantly a *severe febrile illness* with stupor and neurological findings as previously noted. The ultimate correct diagnosis (see below) of suprasellar cyst came as a complete surprise, particularly as there was no suprasellar calcification visible on the plain skull x-ray films.

ABSTRACT OF CASE HISTORY

A. A. (M.C.V.H. No. A-59403), a 4-year-old white male, was admitted to the Pediatric Service, Medical College of Virginia Hospital on Jan. 23, 1945, with a history of a gradual onset of chronic lassitude, weight loss, and anorexia for the previous five months. Shortly after onset of these symptoms, purposeless jerking movements of the upper extremities were noted. By January, 1945, he had developed edema of the eyelids and a "glazed look" in his eyes. The jerking movements were more severe and associated with profuse diaphoresis and gnashing of the teeth. The family physician then referred the patient to the hospital.

Examination by the pediatric service on admission revealed, in addition to malnutrition and dehydration, stupor, irregular purposeless movements of the head, face, and extremities, generalized hyperreflexia, a positive Brudzinski's sign, and questionable Babinski signs, bilaterally. The right elbow joint was painful but not swollen. The clinical impression was a probable chorea of rheumatic origin although encephalitis was regarded as a possibility. A chest x-ray film was

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negative, and an electrocardiogram showed a P-R interval of 0.16 second which the pediatricians felt was somewhat prolonged in this case. Routine blood and urine studies showed evidence of dehydration on admission, but a leucocytosis with a relative increase in the polymorphonuclear neutrophiles was fairly constant on repeated counts. Lumbar puncture showed an initial pressure of 170 mm. of fluid, not a significant elevation in a child noted to have been struggling at the time. Cerebrospinal fluid studies were normal except for a sugar content of 155 mg. per cent and chlorides of 634 mg. per cent. The spinal fluid sugar was redetermined five days later and found to be 114.5 mg. per cent at which time a blood sugar determination revealed only 112 mg. per cent. This finding was strongly suggestive of a virus encephalitis.

On Feb. 9, 1945, neurosurgical consultation was requested, and examination by one of us (A. C. J.) revealed a semistuporous, markedly spastic, and emaciated child, staring vacantly, and intermittently blinking his eyes rapidly. All extremities were moved on stimulation. The deep tendon reflexes were equally hyperactive and associated with bilateral ankle clonus and Babinski signs. The pupils were fixed to light and dilated, but extraocular movements were intact. The fundi were normal.

On the basis of the febrile course, bilateral pyramidal, extrapyramidal, and brain-stem signs, with a high spinal fluid sugar, the initial impression was "virus encephalitis." The possibility of a brain-stem tumor was mentioned at that time but considered unlikely.

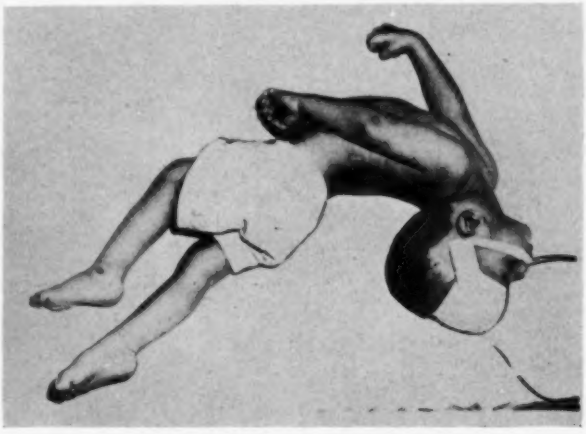

Fig. 1.—Apparently moribund condition of 4-year-old child at time of first ventricular tap, which was the day before verification of the suprasellar cyst. It was thought at this time that the child probably had a brain stem (pontine?) glioma.

Skull x-ray films were negative except for "moderate convolutional atrophy with widened sutures and thin skull vault." No suprasellar calcification was noted, nor were there significant changes in the sella turcica.

Neurosurgical consultation was again requested on March 22, 1945, at which time he was noted to have become progressively worse and now showed a slight cranial enlargement with Macewen's "cracked-pot" sound and bilateral papilledema of 4 diopters. Our impression was changed to brain-stem tumor for the reason stated in the introductory remarks, and radi-

ation therapy of the brain-stem was advised. Because of the high degree of increased intracranial pressure, suboccipital decompression was considered preliminary to radiation, but it was decided that his condition would not permit any extensive surgery. As a compromise, bilateral anterior burr openings were made to afford access for ventricular puncture, should signs of acute ventricular obstruction develop during the course of radiation.

tory embarrassment with a temperature of 104 to 105° F., coarse generalized tremors, and profuse diaphoresis. Because of his almost moribund condition, immediate puncture of the right lateral ventricle was undertaken (Fig. 1). The ventricle was entered at a depth of only 3 cm. from the scalp, releasing clear, colorless fluid under greatly increased pressure. There was little clinical improvement, and the right ventricle was tapped

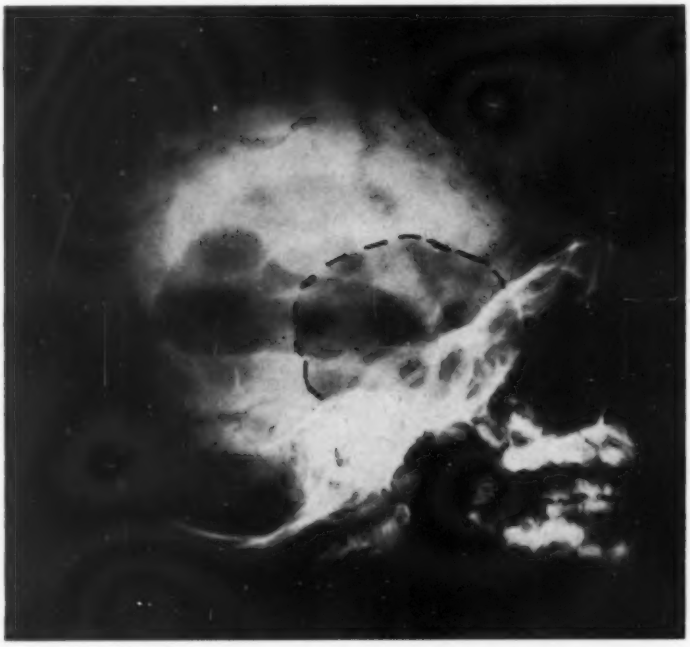

Fig. 2.—Combined ventriculogram and cystogram. The air shown within the dotted line (semicircle) is in the suprasellar cyst; the dilated lateral ventricle can be seen just above and posterior to it.

These trephine openings were made in the frontal region deliberately, because of the critical condition of the patient, to avoid the respiratory difficulties of the cerebellar position under local anesthesia, a most fortunate, albeit inadvertent, decision, as later events proved.

X-ray treatments were begun on March 28, 1945, and three days later the patient developed an acute respira-

again the next day. With the intention of a more complete ventricular drainage, the head was rolled to the right and the brain needle advanced to a greater depth. At a depth of 6 cm., yellow, syrupy fluid suddenly poured from the needle. About 50 c.c. of this fluid was removed, and it contained shimmering crystals, presumably cholesterol, suspended in it. Laboratory studies showed the fluid to

contain 4.5 Gm. per cent (4,500 mg.) of protein and 77 mg. per cent of cholesterol. X-ray therapy to a total of 2,500 r. had been administered by this time. Three days later, a 20 c.c. ventricular air replacement was done, and the brain needle was then advanced into the cyst where 50 c.c. more of yellow cystic fluid was removed and replaced with air. X-ray films clearly demonstrated the combined ventriculogram and "cystogram" (Fig. 2).

Within two weeks, marked improvement was noted, and about two months later, June 6, 1945, he was discharged, at which time he was walking, talking, gaining weight, was alert, and was physically active (Fig. 3). Papilledema was no longer present and there was only moderate bilateral spasticity.

Fig. 3.

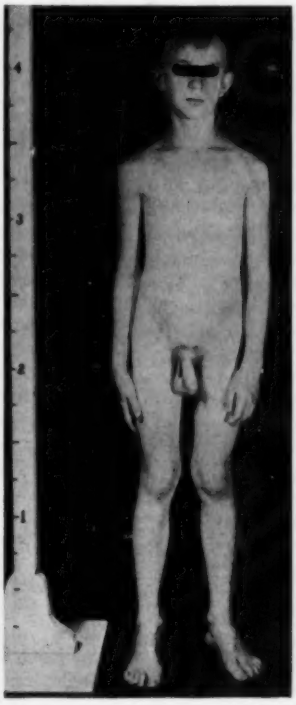

Fig. 4.

Fig. 5.

Fig. 3.—Condition of child at time of first discharge from the hospital when he was able to walk and talk and was active physically. This was approximately two months after the suprasellar cyst was first drained (compare with Fig. 1).

Fig. 4.—Child, aged 7 years, shows adult type of external genitalia. This was approximately three years after the suprasellar cyst was originally drained; signs of pubertas precox first appeared approximately a year previous to this photograph when child was aged 6 years.

Fig. 5.—Child, aged 9 years (Feb. 1, 1950) approximately five years after original suprasellar cyst drainage. Pubertas precox is obvious. Patient is in excellent condition, attending school regularly.

He was followed at intervals in the Out-Patient Clinic, and on September 21, 1945, he was readmitted to the Neurosurgical Service because of symptoms of recurring increased intracranial pressure. X-ray therapy was resumed, but by October 17 his

physical condition had progressively deteriorated to the extent that it was decided to attempt another drainage of the cyst.

The right lateral ventricle was large and the ventricular fluid was again observed to be under considerably increased pressure, but the cyst could not be located with the ventricular needle. Signs of meningitis developed, but as smears and cultures of the ventricular fluid were repeatedly negative for organisms, it was felt that some leakage of the highly irritating cholesterin-containing cystic fluid into the ventricular system had provoked a meningismus. On October 24, the cyst was successfully entered and 52 c.c. of dark, amber-colored, syrupy fluid was withdrawn. Air studies were repeated, with results as striking as those obtained during the first hospitalization. Subsequent recovery was again rapid, and the patient was discharged ambulatory and neurologically, considerably improved.

Since then he has been followed frequently in the Out-Patient Clinic. At one of these examinations (Sept. 8, 1948), the child showed no signs of increased intracranial pressure and was in good general health. There was some apparent frontal lobe disturbance, suggested by aimless overactivity, lability of attention, and facetiousness. Moderate bilateral secondary optic atropy was present, with a visual acuity of O.D. 20/50 and O.S. 20/30, and a right exotropia of 25°. The skull films at this time were normal except for slight, convolutional atrophy with very faint, questionable, spotty calcification in the suprasellar region observed for *the first time*.

There has also developed a striking degree of pubertas precox, first noted by the child's mother within a few months after his last hospitalization (about two years after the onset of the initial symptoms), and progressing to a genital development of at least that of a 13- or 14-year-old boy, the child then being 6 years of age. Fig. 4 illustrates this condition on April 17, 1948 (aged 7 years). At the end of another year, sexual characteristics were fully developed. Fig. 5 shows the condition of the boy (aged 9 years) on Feb. 1, 1950, at which time he was in excellent condition, attending school regularly.

Final Progress Note.—The child developed convulsions in 1949 and other attacks in which he would whirl violently and fall to the ground. These were unassociated with headache or vomiting. Phenobarbital and Dilantin therapy was begun. The last few examinations may be summarized as follows:

1. Feb. 1, 1950. Patient is alert and cooperative. Optic discs well outlined, although pale. Going to school regularly.

2. May 3, 1950. Patient has had an occasional convulsion since being seen three months previously. Dilantin increased to 0.1 Gm. t.i.d. Optic discs well outlined. Child going to school regularly. Counts fingers accurately with each eye. There is no diplopia or extraocular palsy. All the extremities are moved equally well. No Babinski sign is present. There is an abortive ankle clonus on the left side; very active and muscular in appearance. No subjective complaints; requires no medication for headache. The occasional convulsion was attributed to the hydrocephalus (?) incident to the suprasellar cyst rather than to a refilling of the cyst itself.

May 17, 1950. A letter from the boy's mother (five and one-third years after first being admitted during his severe acute illness) states that he was in excellent condition, had had no further convulsions, or other complaints, and was attending school regularly.

Sept. 6, 1950. Child examined in Out-Patient Department. No convulsions for last three months. Little or no headache. Counts fingers accurately with each eye. Optic discs pale and well outlined; extraocular movements excellent. Tendon reflexes are

moderately brisk, although there was no ankle clonus or Babinski sign. He was attending school regularly.

DISCUSSION

It is a well-known neurological fact that intrinsic tumors of the brain stem are generally late in producing signs of increased intracranial pressure. Because of the chief findings of bilateral spasticity, pyramidal tract signs and cranial nerve involvement (particularly in those patients in which there is any disturbance of body temperature), such tumors are often misdiagnosed as encephalitis until papilledema or other pressure signs supervene. This point is well emphasized by Bailey, Buchanan, and Bucy.[3]

By good fortune, the unsuspected suprasellar cyst was entered while tapping the right lateral ventricle for relief of acute increased intracranial pressure signs during the course of x-ray therapy. Subsequent air replacement of both ventricular and cystic cavities resulted in excellent roentgenographic demonstrations of the cyst and its anatomical relationships (Fig. 2).

Spontaneous filling of suprasellar cysts by air due to erosion into the sphenoid sinus,[4] or through intentional air replacement similar to ours,[5] has been observed before.

Erosion of the sella turcica or suprasellar calcification is present in nearly 80 per cent of craniopharyngiomas. While its absence is therefore not very unusual, in this case it unfortunately tended to emphasize those features suggesting an inflammatory process or an intrinsic neoplasm of the brain stem.

We are quite surprised and at some loss to explain adequately the remarkable and prolonged relief of symptoms to date, since the cyst was last drained five year ago. The extensive radiation therapy which the child received is the most likely explanation, although possibly there is at least a slow leak of cyst contents into a lateral ventricle thus decompressing the cyst.

The development of a remarkable degree of pubertas precox is one of the most interesting features of this case. At one time thought to be a diagnostic feature of pineal tumors, it is now well recognized that precocious puberty is not only frequently absent in verified pineal tumors but often occurs in other lesions of the diencephalon and hypothalamus. Whereas pubertas precox, at one time considered pathognomonic of pineal tumors, was present in this patient, it is by no means always so with tumors of Rathke's pouch. Similar changes in the sexual sphere have been recorded with tumors of the hypothalamus, according to Bailey, Buchanan, and Bucy.[6] It is not possible to associate pubertas precox with any one structure. It is, therefore, apparent that this disturbance is not essentially endocrine in nature but is probably secondary to damage involving regulating neuroendocrine centers and pathways in the diencephalic area by various agents (inflammatory or neoplastic) and probably at various sites.

The importance of recognizing that brain tumors in general are rather commonly encountered lesions should be emphasized. One's index of suspicion in favor of tumor should be *high* in cases of this type. Such a possibility must be strongly considered in any progressive neurological disease and such cases should be followed closely, particularly with reference to the development of papilledema or other evidence of increased intracranial pressure.

SUMMARY

A case of suprasellar (Rathke's pouch) cyst is reported, in which the initial history and neurological findings successively simulated (1) rheumatic fever, (2) encephalitis, and (3) brain stem tumor. Aspiration of the cyst, inadvertently at first, and intentionally subsequently, not only afforded dramatic relief of pressure

symptoms, but when combined with ventricular air replacement permitted a striking demonstration of both the suprasellar cyst, as well as the ventricular system radiologically. The patient remains well five and one-half years after initial surgical drainage of the cyst, x-ray treatment also having been given. A remarkable degree of pubertas precox developed postoperatively and this, as well as the prolonged recovery following aspiration of the cyst only and x-ray therapy, is discussed.

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4. Brain, W. R.: Diseases of the Nervous System, ed. 2, New York, London, and Toronto, 1940, Oxford University Press, Fig. 27 (p. 235).
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Erratum

In the article by Dr. David Goldring entitled "Neuroblastoma Sympatheticum With Metastases" on page 231 of the February issue of the JOURNAL, the legend to Fig. 2 should read:

Fig. 2.—Typical rosette formation as seen in liver biopsy section. Note definite rosette formation. Magnification power ×10.

Medical Progress

UROLOGIC CONSIDERATIONS IN PEDIATRICS

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NEW YORK, N. Y.

THE ever-widening clinical recognition and treatment of urologic conditions in infants and children are sharply reflected in the amazing increase in contributions on this subject to the literature of disease in the young. Prior to 1930, less than 1 per cent of pediatric articles were concerned with this field; in 1940, not over 3 per cent, but today these contributions constitute nearly 15 per cent. The development of miniature cystoscopes and other special instruments necessary for the examination of the small urinary channels of the young, and the epochal introduction of excretory urography have made possible the complete urologic investigation of even the newborn in both sexes. Yet the educational factor as much as any other accounts for the present general employment of accepted urologic studies and treatment in the young.

During the last score of years, and notably during the past decade, the high incidence of urogenital tract diseases in infants and children and the indications for adequate technical investigation have been stressed to the medical students who are today established clinical practitioners. It is this group, more than any other, who considerately seek urologic assistance for their young patients with clinical manifestations suggestive of urologic disease.

Fortunately for juveniles, many older physicians, and pediatricians in particular, gradually are accepting a similar point of view. But this clinical change-over has been slow, difficult, and has often met highly obstructive and sometimes fierce professional resistance. Even now this modern viewpoint and appropriate cooperation are not everywhere exhibited. On one of the large pediatric services in this county in a community otherwise highly enlightened medically, children are still denied specialized aid in the face of known urologic disease. For example and inconceivably, a child recognized to have a stone in the bladder is permitted to lay on the ward for six months, meanwhile receiving only urinary antisepsis because of the coexisting pyuria. In such a case, not only is the stone itself likely to be a source of distress and illness with continued urinary infection, but the persistence of the even more important peripheral congenital obstruction in the lower urinary tract which predisposed to the stone formation and behind which the calculus lodges, produces back-pressure injury of the proximal urinary system. Of greatest importance is the damage of the kidneys which commonly is augmented by complicating persistent infection. Yet the removal of such a stone and of the urinary obstruction is easily accomplished with only minor

risk to the child, the urine is far more readily sterilized, and the prognosis is correspondingly enhanced.

The possibilities for the development of grave urologic disease is suggested by the observation at autopsy that 10 to 14 per cent of all individuals are born with some form of urogenital tract anomaly. Many of these lesions are mild and of scant clinical importance, yet many are multiple and an important number threaten life.

Studies have shown infants and children to be heir to practically every urologic disease known to adults, even cancer of the penis. These young patients with urologic manifestations require complete investigation to establish the anatomic diagnosis exactly as do adults with similar symptoms or clinical picture. Moreover, several conditions and clinical syndromes which in the past have been considered to be strictly medical problems and often therapeutically hopeless, have been found to result from urologic disease, particularly of the kidneys. Here the disease in the kidney has resulted chiefly from unrecognized urinary obstruction (in children this is nearly always congenital) which is commonly complicated by infection, and cure will largely rest upon eradication of the interference with urinary drainage. Thus hypertension has frequently has been relieved by (1) removal of the obstruction, either supravesical or infravesical, or (2) by excision of a unilateral hypoplastic kidney (Goldblatt mechanism), congenitally so or the result of long-standing atrophic pyelonephritis. Retardation of growth often falls in this etiological category when total renal damage is extreme and the function is minimal, the late manifestations being those of so-called renal rickets. Gastrointestinal disturbances are outstanding in at least half of all cases of major uropathy in the young, and for some time may be the only manifestation of the underlying urinary tract disease. It is therefore apparent that not all children with urologic disease will pass blood, strain to urinate, have urinary frequency, renal or abdominal pain or tumor. In the clinical study of the patient, the urinary tract always merits prominent consideration in appraising the over-all picture.

The young tolerate urologic examination better than their elders and no child should be denied the benefits of present-day urologic investigation when the indications for such a study are present. A life of preventable invalidism is the lot of many children thus denied urologic examination and treatment; many of these seemingly hopeless conditions are curable and improvement can be achieved in many more cases. Those denied represent the fruits of medical neglect.

As these studies in the young have extended, the number of clinical conditions calling for urologic investigation has grown to include the following, the presence of which may be considered an indication for thorough examination; other conditions which merit such study are observed from time to time, for example, chyluria.

1. Pyuria.
   a. Acute persistent.
   b. Chronic.
2. Disturbances of urination—dysuria, frequency, urgency, etc.
3. Hematuria (except acute nephritis).
4. Abdominal pain.
5. Abdominal tumor.
6. Anomaly of external genitalia.
7. Urogenital injury.
8. Hypertension.
9. Renal insufficiency.
10. Enuresis.
11. Spinal cord injury and disease.
12. Retarded growth.

The most important of these will be briefly discussed and particularly as their presence and/or persistence are indications for adequate urologic examination.

Urinary Infection.—The dominant lesion in urinary infection must always be considered to be in the renal parenchyma until proved to be elsewhere. While the clinically convenient designation of pyelitis is usually applied in these cases, the histologic picture is generally interstitial suppurative nephritis, in which associated infection and inflammation of the renal pelvis is relatively mild and of little clinical concern.

Urinary infection is nearly always manifested by pus in the urine but in rare instances pyuria may exist without demonstrable infection. Amicrobic pyuria may result from nonbacterial congestion, obstruction, calculous disease or, as has lately been suggested, virus infection. Proper collection of the urine specimen for examination is the sine qua non (1) in establishing the nature and probable severity of the disease, (2) for precise identification of the bacterial invaders, (3) for intelligent guidance in therapeutic progress and, finally, (4) as test of cure of the infection. For this reason, the voided urine from a female is worthless for study in urinary infection, either as to the amount of pus present or the bacterial invader. Aseptic catheterization should be employed in urine collection in females of all ages and also in the male when satisfactory aseptic collection cannot be achieved by voiding. The demonstration of more than 3 to 5 leucocytes per low-power field in the uncentrifuged specimen may be considered abnormal.

Acute urinary infections are generally self-limited and clinically disappear in seven or ten days irrespective of treatment, but the patient cannot be considered cured until at least two negative cultures of properly collected specimens have been obtained. Failure to observe this dictum will mean the persistence of smoldering asymptomatic infection in half of the patients, in whom exacerbation of the urinary infection frequently occurs consequent to intercurrent debilitating disease, acute focal infection, severe chilling, urinary obstruction, and so forth. The diagnosis "recurrent acute pyelitis" is then commonly made. The clinical history of many children with persistent pyuria discloses their lives to have been dotted with such recurrences.

When acute infection remains severe with high temperature, prostration and/or sepsis and with no apparent response to therapy in seventy-two hours, a complete urologic investigation is demanded at once. Most often this will reveal acute infected hydronephrosis which is usually engendered by congenital upper ureteral obstruction, notably ureteropelvic junction stricture. Even more severe surgical lesions frequently exist in "persistent acute pyelitis" and include pyonephrosis, massive focal renal suppuration, renal thrombosis or perinephric abscess. In short, only by timely investigation and adequate surgical therapy can the lives of these extremely sick children be saved. Fortunately, the early and intensive administration of chemotherapeutic agents and antibiotics has materially reduced the incidence of grave suppurative renal complications.

Chronic urinary infection is often an accidental discovery at the time of

physical examination performed periodically or routinely as at school, or for symptoms apparently unrelated to the urinary tract. In most instances it is the sequela of inadequately treated acute urinary infection of the distant past. Complete urologic examination should be carried out in these cases if intensive urinary antisepsis for two to three weeks fails to eradicate the infection as evidenced by analysis and at least two negative cultures of properly collected specimens. In our experience examination of infants and children with persistent pyuria has disclosed practically every urologic lesion known to exist in adults except epithelial neoplasia of the urogenital organs. Should the urine of the patient with chronic pyuria be sterilized by intensive chemotherapy, he should not be discharged as cured until at least a satisfactory excretory urographic study has demonstrated the urinary tract to be architecturally normal. This implies the absence of obstruction or other condition which predisposes to or helps to perpetuate urinary infection, the presence of these predisposing factors being suggested a priori by the chronicity of the infection. Treatment will be based on the diagnostic findings and may be conservative by intensive chemotherapy aided by periodic progressive dilation of stricture, for example, or radical by major surgery. Nephrectomy is required in a large number of children whose pyuria is of unilateral origin from a hopelessly diseased kidney. Having corrected the anatomic lesion, the patient should not be discharged as cured until the urine has been sterilized.

Disturbances of urination include dysuria, urinary frequency, urgency or strangury, and usually reflect urinary infection or inflammation although congenital obstruction at the bladder outlet or peripherally commonly exists. Stenosis of the external urethral meatus is the commonest single cause in both sexes. Foreign bodies such as a hairpin which the child has introduced, or a vesical stone may be revealed by the examination which is demanded by persistence of these symptoms for four weeks.

Enuresis is one of the commonest vesical disturbances and is doubtless a functional manifestation in over 95 per cent of the patients, reflecting maladjustment of the child, his response to insecurity, resentment, and so forth. Normal bladder control is rarely acquired before the thirtieth month and we seldom advise urologic examination because of enuresis in children less than 4 years of age. When enuresis persists for three or four months despite intensive medical treatment and psychotherapy, urologic study should be carried out. In over 1,500 enuretic children in this therapy-resistant group thus investigated, urinary tract disease adequate to explain the incontinence was disclosed in nearly two-thirds. Sometimes the lesions found have been of vital importance. Lower urinary tract obstructions, predominantly congenital, have been the largest single-type conditions disclosed. While it may be argued that these children did not have true enuresis, and this is readily granted, the fact remains that they were treated unsuccessfully for months and years by, in most instances, extremely capable clinicians. Some patients, not given the benefit of urologic study, acquire urinary continence as they grow older but the basic condition remains. We urologists encounter in their teens and

twenties a discouraging number of these former enuretics with congenital contracture of the vesical outlet, a large bladder residuum, or other lower tract obstructive lesions which should have been recognized and corrected in childhood when the patient was enuretic. When the urologic examination discloses no organic disease to explain the incontinence, psychotherapy and medical measures may be continued with the comforting assurance that no organic urinary tract disease exists.

Hematuria in the young is most commonly due to acute urinary infection, acute nephritis, ulceration of a stenosed external urethral meatus, urinary tract tumor, and in this order, yet there are more than fifty potential causes. Complete urologic investigation should be carried out in all cases of hematuria except in acute nephritis. Hematuria due to infection alone requires intensive chemotherapy or antibiotic therapy while obstruction, calculus, or tumor demand appropriate treatment. Hematuria is relatively common with hydronephrosis and other obstructive lesions and results largely from congestion of the urinary passages above the point of blockage and/or complicating infection.

Abdominal pain commonly reflects disease of the urinary tract and especially of the obstructive variety which in the young is predominantly congenital. Congenital ureteral stricture and secondary renal back pressure have been observed to cause abdominal pain more often than any other urologic lesion. Reflex disturbances of the gastrointestinal tract frequently ensue and are present in over half the children with chronic urinary obstruction and/or infection. Treatment will be based upon the findings of urologic study which is essential in these cases. With eradication of the pain-producing condition, not only will the digestive upsets disappear but the child will rapidly gain in appearance, strength, and weight. Yet he is not cured until the urine has been sterilized.

Abdominal tumors may appear even in early infancy; hydronephrosis is the commonest abdominal tumor of childhood with renal embryoma (Wilms') and neuroblastoma of the adrenal second and third in incidence, respectively. Palpable hydronephrosis in the young is usually due to ureteropelvic junction obstruction. All hydronephroses demand prompt recognition and treatment that the kidney or kidneys may be salvaged. When the mass is a renal or adrenal tumor, the earlier the diagnosis is made and the neoplasm removed, the better the prognosis becomes. Congenital palpable polycystic renal disease is extremely rare, but in all of these tumor-producing conditions the anatomic diagnosis cannot be accurately made without urologic investigation and particularly retrograde pyelography, preferably bilateral. I strongly disfavor diagnostic reliance upon excretory urography or as a surgical guide when the problem is operative treatment of the upper urinary tract for obstruction or tumor.

Anomalies of the external genitalia are extremely frequent in the young. Because in about one in three of these cases the upper urinary tract is also anomalous, its investigation should be carried out, if only to the extent of satisfactory excretory urography.

Urogenital injury always demands at least a definitive excretory study to

determine the integrity of the urinary tract, particularly to identify a point of rupture and whether urinary or hemorrhagic extravasation is present. When (1) the excretory examination is unsatisfactory, (2) the condition of the patient is grave and, especially, (3) if there is continued profuse hematuria, prompt complete instrumental investigation is imperative that proper surgical treatment may be instituted at once to save the patient. In urethral rupture following straddle injury for example, the immediate establishment of free bladder drainage by indwelling catheter will often forestall urinary extravasation and periurethral phlegmon. Yet such conservative measures in serious urinary tract injury must not be continued unless the condition of the patient shows satisfactory response.

Injury of the spinal cord requires urologic study. Following cord injury the urologic examination should be delayed until the condition of the patient has improved sufficiently to warrant the investigation; meanwhile free vesical drainage is maintained by indwelling catheterization or cytostomy. Excepting birth injuries from which the patient often promptly dies, cord injuries are comparatively rare in the young and result chiefly from traffic accidents or falls. Weeks or months later when the neuromuscular status of the urinary tract has been evaluated, transurethral resection of the vesical outlet when indicated often restores adequate control and forestalls progressive renal injury.

Neuromuscular disease of the urinary tract not caused by trauma is of high incidence in children in whom it is generally consequent to vertebroneural malformations (spina bifida, meningocele, myelocele, meningomyelocele) but may be occasioned by infections, inflammations, or degenerations of the nervous system (anterior poliomyelitis, transverse myelitis, syringomyelia, diphtheria, and so forth). Such children require both comprehensive neurologic and urologic study. Unfortunately, in most of these children neurosurgery has little to offer and the urologist must often be content only to maintain free urinary drainage and to control urinary tract infection. While the long-term prognosis in this group is usually poor, chemotherapy, antibiotic therapy and, in properly indicated cases, transurethral resection of the vesical outlet or permanent cystostomy, today offer new hope for many children so afflicted.

Renal insufficiency in the young is often due to congenital paucity of the kidney parenchyma: bilateral renal hypoplasia or congenital absence of one kidney with renal hypoplasia on the opposite side. Insufficiency may also be the result of severe antecedent renal disease such as nephritis or of long-standing urinary obstruction and infection or both. The clinical manifestations may not appear until the fourth or fifth year of life and are generally those characteristic of nephritis, with or without hypertension, but sometimes present only as growth retardation. The functional and morphologic status of the kidneys in chronic nephritis as well as anatomic renal insufficiency can be accurately determined only when adequate urologic examination is part of the diagnostic study.

Retarded growth commonly reflects advanced renal disease or deficit as

described in the preceding paragraph; in many cases complicating urinary infection accelerates the renal damage. The earlier the renal disease appears and the greater its severity, the more striking will be the physical retardation. The skeletal changes in these children become predominantly those of osteitis fibrosa cystica, the condition often designated as renal rickets. It is advised that all undersized children and those whose growth is abnormally slow have at least the advantage of a satisfactory excretory urographic study to determine the anatomic integrity and physiologic function of the urinary tract, especially the kidneys. Usually, and on the basis of this preliminary urographic study, conditions are found which demand further investigation by complete urologic examination. Such conditions as congenital contracture of the vesical outlet, congenital valvular obstruction of the prostatic urethra, congenital hypertrophy of the verumontanum, some forms of neuromuscular vesical disease, and so forth, can be recognized only by cystoscopic study. When the urinary tract disease is remedial and is corrected, the child is offered a chance to grow; the longer the renal deficiency persists, the greater will be the growth handicap. Most of these children ultimately die in uremia.

Hypertension due to unilateral renal disease has been observed in about 1 per cent of patients with hypertensive vascular disturbance subjected to complete urologic study. One kidney and its blood supply is sometimes congenitally hypoplastic and the pathologic picture closely resembles that of the experimental Goldblatt kidney. The renal disease may be late sclerotic chronic pyelonephritis. In advanced unilateral renal disease with associated hypertension, nephrectomy has frequently been followed by fall of blood pressure to more normal levels, but cure should not be assumed unless the diastolic pressure in particular remains within normal limits for at least two years. Nephrectomy should not be performed because of hypertension alone but solely on the basis of the existing renal pathology. In short, the kidney is removed because it should be and would be if the blood pressure were normal.

SUMMARY

A more widespread recognition is urged of the potential importance of symptoms of urinary tract disease as well as of the indications for urologic investigation in the young. Willingness of the medical advisors of these patients to have urologic study made when indicated will nearly always lead to the institution of specific urologic treatment, conservative or radical. This may be expected to avert much needless suffering and often the likelihood of an early death. Many children can be saved from the doom of a life of invalidism and the parents spared the heartache, despair, and economic burden such illness entails. Fortunately, most of these children can be cured or rehabilitated and preserved for useful lives.

Psychologic Aspects of Pediatrics

THE MANAGEMENT OF "INFANTILE INSOMNIA"

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OF THE sleep disorders in children, the most common are difficulty in getting the child to sleep at night, waking in the night, or both. While such problems are fairly common in a mild form which are not too distressing to the parent, there are severe cases where one finds the parents badly distraught and much in need of help. These two types of wakefulness might well be termed "infantile insomnia."

It is the purpose of this paper to outline a management regimen for these severe cases. No great effort will be made to explain why these children are having insomnia, as there are probably many factors involved and individual problems in each case. However, the assumption can be made that there is an element of separation anxiety in most cases and, as will be seen, the methods of treatment to be presented are based largely on that premise.

The children that we would label infantile insomniacs may be divided into two groups, first those who fight off going to sleep in the evening and, second, those who awaken one or more times during the night. We are not concerned here with the older children who do not seem to want to go to bed. In this latter group the problem is usually a disciplinary one with the child testing his parents' ability to set his limits and to see if they can make him go to bed. This is a result of the parents' own indecisiveness over a long period of time. The group we are speaking of is younger, usually 6 months of age through the third year. In this age period there are many children who go through a period of being difficult to get to sleep, or who awaken at night, but do not disturb the parents too greatly. It is fair to say that in any problem of this type the severity may be gauged by the degree of distress of the parents. In the milder cases which are not too distressing to the parents, a detailed management such as we are discussing here would be superfluous.

SEPARATION ANXIETY

If the child is awake a good part of the night, the parents are robbed of adequate sleep, with the usual consequence of nervous tension, which, in turn, aggravates the child. They become impatient with the child and usually disagree between themselves as to what should be done about it and how the child should be managed. One gets the picture in these severe cases of a tense home that really needs help.

This problem is primarily an emotional one. Usually the child shows signs of separation anxiety in that he raises a fuss when left alone but will

remain quiet if the parent stays in the room. Often, these children show an unusual need to have a parent in sight all through the day. Without going into any involved analysis of the reasons for this behavior, it seems logical that the child has a sense of insecurity and, realizing his dependence, has a fear of being deserted and unprotected if he sleeps.

This situation is often found in a home that is obviously unbalanced emotionally. But it can be a severe problem in homes that seem sound and on an even keel.

When the parent seeks help for a sleep disturbance in her child, it is well to do a complete physical examination before discussing the sleep problem in detail. The parent often feels there is some physical defect, and probably almost wishes one would be found, because a physical ailment is less challenging and less mysterious. Usually, the physical examination is negative but it is essential as there are numerous physical factors that may disturb a child's sleep. Moreover, examination gives the physician an opportunity to get the feel of the type of child he is dealing with.

Common ailments that are disturbing to the child at night are pinworms, meatal ulcer, anal fissuring, eczema, scabies, chronic vasomotor-rhinitis and difficulty in breathing, such as is seen with extreme enlargement of the adenoids.

HISTORY TAKING

The history should begin by letting the parent tell in detail the nature of the wakefulness on the child's part and learning of the child's willingness to go to bed, how soon he goes to sleep, what time he awakens, how long it takes to go back to sleep, and how many times he is awake. At the same time, it will come out what the parents have been doing about his problem and how they feel about it. If the trouble has gone on for some time, it is likely that they have tried many different approaches and have had many different attitudes. The fact that they are seeking help means that these have all failed. Of course, these failures have aggravated the situation, both for the child and for the parents. Further discussion will bring out the nature of the child during the day, how he feels toward each parent, siblings, and other persons with whom he has contact. It is also important to know whether the child shows apprehension in the presence of strangers or in a strange environment, and if so, if he is often exposed to such situations. This will help gauge the child's need for security.

Though it is important to inquire whether the onset of the child's poor sleep habits can be related to any incident such as a change of residence, it is common to find no definite date or incident to tie to, but just a gradual worsening of the sleep habits.

The usual routine past history including pregnancy, labor, newborn period, feeding, development, and illnesses should be gone into and any phase that seems pertinent enlarged upon.

It is essential to inquire, at least superficially, as to the emotional situation between the father and mother. Often, if the parents are unhappily married, they will tell you so, and if such be the case, it is more than likely that the home atmosphere is not all that could be desired and certainly not conducive to a feeling of security in

the child. If the situation is quite bad and shows little hope for betterment, one gets the feeling that he is not going to be too successful in helping them with the problem for which they came to you.

In addition to learning something of the parent's feeling for each other, it is important to learn if they differ very sharply on how to meet this and other problems which their child presents. If there is a marked divergence of opinion, it makes for a bad prognosis, not only for the child's sleep problem, but also for the child's entire personality development.

After going into the matters already discussed, one should inquire about the physical set-up of the home, whether the family is in an apartment or in a home by themselves, and whether the child has his own sleeping room. If the child creates a disturbance at night and the family is not in a dwelling alone, the problem is aggravated, especially if the child does much crying. Under these conditions a special effort is made to quiet the child and often the greater the effort the more noise he makes, because the increased effort reveals itself to the child as anxiety in the parent. This tends to increase the child's fears, if that is his trouble. If his disturbance represents a hostility toward the parent, the greater response from the parent means success in his hostile motives, so he carries on more lustily than ever. The parent's concern is twofold: one, that his child disturbs the neighbors' sleep and, second, the natural feeling of embarrassment that any parent feels of having others know that he is having a problem with his child.

As a rule, people live in the best circumstances possible for them, and, further, they have a desire to live on a better scale. As a matter of fact, this is often the basis for a family conflict. Since the dwelling probably cannot be changed, one may only aggravate an already existing conflict by attaching too much importance to this matter, and so it is probably best to play this down. With proper resourcefulness, these handicaps can often be overcome. If, however, the family have very definite prospects for improved housing, there can be no harm, and often much help, from telling them that they can look for an improvement when they move. There are exceptions, as for example, when the couple have been satisfied apartment dwellers, and when a child comes along, they expect him to fit in with their old way of life, which in a way is an easy irresponsible one. If such is the case and they have the means to live alone, they should be told to get out and look, that they owe it to the child and to themselves.

SITTERS

Another avenue of investigation is the family's social life and with whom they have to leave the child. It seems that our culture encourages each segment of the family to assert its independence and does not expect help in return. As a result, one sees more and more married couples calling upon outsiders to care for their children when they are away. "Sitters" they are called. The point we are leading up to is that people need to get away from home. They do need outside interests; some more than others, some too much. But forcing them to stay home too much will heighten a hostility to their home situation and thus make it more difficult for the child. On the other

hand, the child, with his feeling of dependence, cannot feel secure unless he is being watched over by someone he *knows*, and he cannot get to *know* any person in a day. Some children are more susceptible to this insecurity than others and one sees children being left with just anybody at any place and yet seemingly not suffer from it. Here one must remind oneself of the individuality of children and that their needs are quite different.

It is common practice to leave the children with a teen-age girl and often a different one each time. The girl may be entirely responsible, but the child does not *know* her. Since this is an important matter, it is well to encourage couples to make every effort to have one person with whom they will leave the child, preferably a grandmother or other relative. If, however, it is necessary to use an outsider, they should make every effort to find one satisfactory person and then find some excuse to have this person in the home on several occasions when the parents are home. One way to do this is to have her in to dinner several times. One can tell the parents that, when this person becomes intimate enough with the family to enter the house without knocking, by that time the child will *know* his "sitter" and will feel secure under her care.

MANAGEMENT

After you have the picture of the problem, you are ready to advise the mother on a program that will help her. It is important to emphasize that your advice is going to help her. This must not be stated too positively lest slow response or delay in improvement give the mother a feeling of failure. The parents should be told that this is an emotional problem that has gone on for some time and that improvement can only be expected to come slowly. Also, that when there is improvement, one must carry on with the treatment methods for some time lest the child relapse.

It is comforting to the parent if she knows that you understand the problem. Instilling confidence is best achieved by stating simply and sympathetically that you realize the seriousness of the problem and are well aware of the emotional strain brought on by a sleepless household. Another point that helps the parents' morale is to point out that their problem is not an uncommon one.

GIVING THE PARENTS INSIGHT

The parent should be told in a brief, concise manner how the problem came to be. You might call this giving them insight into the problem: For the first six to eight months of life, the child does not identify his caretakers or his surroundings and probably would have been content with anybody that gave him comfortable affectionate care. But somewhere near the beginning of the second half year, his intellect grows to the point where he recognizes and identifies his environment and those persons in it. About this same time, he comes to realize his own utter helplessness or dependence on others for care and protection. Naturally, it is those persons whom he first knew that he trusts most and so he is fearful of strangers and strange situations. It should be understood that, although the infant's language faculty is primitive, he is able to perceive feeling tones

better than he will be able to later on when his perception has been varnished with many coats of cultural veneer. And so, if you, his caretaker, have apprehensions, anxieties, or tensions, the infant will perceive them and translate them into a feeling of insecurity. Thus, insecurity is not necessarily related to love as so many people are led to believe from popular writings. It must be emphasized that all children are as different in detail as we adults, and these feelings are more pronounced in some children than others. Because a neighbor can neglect her child and seemingly get away with it, does not mean that your child is not just as strong as her child. It is only natural, that one way in which the small child will manifest his fears and feelings of insecurity is to fear being left alone, especially in darkness, and he will fight off sleep because of his fear of the unknown while he sleeps.

This is an attempt at a simple explanation of separation anxiety which is meant to give the worried parent some insight into the reasons for the child's behavior and probably is the correct and entire explanation in most cases, if one accepts the thesis that for the most part the child's behavior reflects separation anxiety. No doubt, there is an element of hostility in many cases and that hostility is most often the result of the rejection of the child by one or both parents. Be this as it may, one must not even intimate to the parent that he has or is rejecting the child without an involved preliminary analytic preparation which the ordinary practitioner is not competent to do. This suggestion must be avoided lest repressed neurotic feelings be heightened in the parent and everybody is worse off than before.

It is well to discuss the parents' attitude toward the child's lack of cooperation in regard to sleeping. As was said before, the history will usually bring out that the parents have tried many methods of management and simultaneously have gone through many attitudes toward the problem. At some time or other, one or both parents have treated the matter as a disciplinary problem and have gone the gamut from stern talk to spanking. One should try to sell tolerance to the parents as the keynote of their approach and ask them to assume that it is not just bad behavior on the child's part. If the parent is discipline minded, it should be pointed out that t h i s approach seldom gets results, which he may already have learned by experience. His best chance of success will be to try to see the problem through the child's eyes. Again mention that you realize how trying this problem is but there is no running away from it and it must be faced. It would be well to note at this point that, if the physician is trying to put across to the parent the spirit of tolerance toward the child, it is equally essential that the physician be tolerant in his attitude toward the parent.

A point worth making to the parent is that small children show a need for routine which seems to enhance their sense of security. It is true that some children show this need more than others, but we are dealing with more or less insecure children. The routine most important to the child is that of his own care, such as feeding, dressing, bathing, napping, and being put down for the night. However, the routine of the whole family is perceived in

that if the day's activities are alike then the feeling tones of the environment will be alike. It is worth while to ask the parents to make every effort to have the days as much alike as possible during the first month or two of treatment.

SLEEPING ARRANGEMENT

If the child is sleeping in the parents' room and another bedroom is available on the same floor, insist that the child be moved. If no other room is available, then point out to the parent that they can simulate two rooms by setting up a screen between the parents' bed and the child's crib, always leaving it there. To further the illusion of a partition, the parents should avoid talking while in bed unless they are quite sure the child is asleep. Recommend to the parents that they have a dim night light burning at all times so that the room is not completely dark and that they leave the door to the sleeping room open. It will help to have the house quiet and radios within earshot turned down. If the weather is not warm enough to require open windows for ventilation it is best to leave the bedroom windows closed and the blinds pulled while the child is in bed.

For the group of children who are difficult to get to bed and to sleep, the following advice is of the utmost importance: Ask the mother to place in the room a floor lamp of the type that will throw only a spot of light over her shoulder. Place in the room a comfortable sitting chair, preferably a rocking chair. Put the child to bed at the proper time. Then the mother should install herself in the rocking chair and give herself a job to do, preferably something with her hands, such as knitting, darning, or needlework. If she says none of these hobbies interest her, then recommend reading as a substitute. If the father is to do the sitting, he will no doubt have no choice but to read.

The presence of the parent in the room brings the child the security of his protector while he goes to sleep. And yet since the parent has a job to do, he is there to do that job, not because he is afraid the child will not go to sleep. In this way, the danger of the child coming to think that his wakefulness will lead the parents by the nose is avoided. Earnestly ask the parents to try to enjoy this industry and make every effort to have purpose lest the child detect any sham. During this period the parent should pay as little attention to the child as possible, and by all means, should not tell him repeatedly to go to sleep. No effort should be made to keep him under the covers and if he wants to stand up and watch the parent, that is all right too, If he cries too much, it is permissible to tell him to be quiet, but make no mention of sleep.

Point out that this procedure is going to be a little dumbfounding to the child, at least for the first few nights. At first the child may quite obviously keep himself awake trying to figure out what is going on and how long the parent is going to sit there. This is especially so if the problem has been long standing, and so the parent must be prepared for a long sitting session, at least for the first few nights. When the child does go to sleep, the sitter must not leave but should continue on with the same industry until the child has been asleep for at least a half an hour. For the first few nights it would be safer to make this one

hour. If the child should sleep for a few minutes, or appear to be asleep, and then open his eyes to find the sitter gone, it is going to be pretty obvious to him that the parent was sitting there only until he had gone to sleep. On the other hand, if the child should awaken after a short sleep and find the parent still sitting there doing the same thing he has been doing all evening, then the child will have obtained a world of reassurance.

The parents must know from the beginning that this program must be carried out in person every night without fail. In severe cases of long standing, they should be told to think in terms of at least several weeks. In mild cases, a shorter time may do. They can plan, however, on having improvement in a week or two and then they will be sitting a shorter time each evening.

In management of wakefulness during the night the parents should be advised thus: Go to the child as soon as you hear him awake, but in an unhurried and calm manner. While approaching the child, and all the time you are with him, talk in a soft voice. Disregard what you are saying because the child will not listen to what is being said anyway. He will, however, be listening to your tone of voice and taking note of your mood. By your presence, he has learned that his protector is on the job; and from your talking, he has learned that you are unafraid and you are not angry. Assuming that the child has a fear or fears, it is most important that he know that you are there and that you are not afraid. But if he had to learn this at the expense of bringing an angry or impatient parent to his bed, it goes without saying that he does not have a very comfortable feeling about the whole thing. Consequently, it is paramount that the parent do the job in a pleasant, uncritical way.

If the child seems quite upset, he may be picked up for a few minutes, but no more, even though he cries after being put down. If he is not too disturbed, avoid picking him up altogether. It is important to have some apparent purpose for being in the room, other than reassuring the child, in an effort to avoid having the child realize that his wakefulness and fears are what brought you to him. Two things to do, and if done slowly enough, will take sufficient time. One is to straighten out his bed covers, and the other is to put a dry diaper on him.

After ten or fifteen minutes have elapsed, the child has become fully awake and oriented and has had ample opportunity to learn that his fears are groundless. With a kiss and an affectionate pat, the child will usually go right back to sleep. If you are dealing with a stable child, and if his wakefulness is due to some isolated fear-provoking episode, he will soon stop awakening. On the other hand, if you are dealing with a basically fearful child, he may well go on waking one or more times a night for a long period.

If the child stays awake but is quiet and not disturbing anybody, he should be left to himself. Parents who repeatedly tell their child to go to sleep may teach him in this way that wakefulness can be an attention-getting device. On the other hand, if the child stays awake but cries, we must assume that this is hostile behavior and it would be best to let him have it out with himself with no response coming

from the parent. In severe cases, this is a big order in itself and can be a real trial for the poor parents. Exactly where fear ends and hostile behavior begins obviously is somewhat of a guess and people vary in where they would draw the line. The parent needs some rule of thumb to go by and it is fair to tell him that, when he has conscientiously carried out our instructions, he can feel he has done everything possible to allay the child's fears and from there on it is behavior. It must be emphasized to the parent, that patience and tolerance must still be his manner. If thirty to forty-five minutes later the child is still crying, it would be well to go to him again and in firm but not angry words tell him to quiet down. Then if the parent has self control to the extent that he can still say he is not in a temper himself, a spanking may be in order and may help. It may be given as a general rule that parents who do not spank children until they, themselves, have lost their tempers, should never spank children, and this rule is just as applicable to this problem as it is to any other.

There is no exception to the rule against taking the child into the parents' bed in order to get him to go to sleep. Usually, by the time people seek outside help for this problem, they have already tried this method and learned its drawbacks.

Sedation alone would be the easy way to temporarily alleviate the problem we are discussing and is often the treatment the parents would like you to give. Obviously, it is not the whole answer but sedation has a definite place as an aid, providing proper emphasis is placed on the points already discussed. Because many children will take large doses of phenobarbital and fight right through it to demonstrate their anxiety, it should be pointed out that the detailed management outlined above is the most important part of the treatment. However, parents and child, because of their mutual frustration and lack of sleep may need sedatives in the initial period in order to help break this vicious cycle.

I usually prescribe one-half grain phenobarbital tablets and do not hesitate to tell the mother to give the child one tablet and take two herself. As a rule, a touch of humor is acceptable. For the group who give trouble at bedtime, use phenobarbital at dinner time. For the group who awake during the night, give phenobarbital at bedtime. For those children who react adversely to phenobarbital, other barbiturates or sodium bromide may be used.

The use of *harnesses* to keep the child lying down in bed should not be advocated as a routine in the management of these children. As a matter of fact, many of these problems have been aggravated by the parent showing undue concern that the child keep properly covered. However, an occasional child seemingly gets a sense of security from the physical restriction of a bed harness. One such child who showed little or no improvement on the regimen outlined here immediately mended her ways when put down with a restraint. No attempt will be made here to tell how to anticipate such a need in a child, but the suggestion is offered that this might be tried as an adjunct if the treatment outlined is not meeting with success.

Comments on Current Literature

CONGENITAL DAMAGE OF THE NERVOUS SYSTEM BY AN ARTHROPOD-BORNE ENCEPHALITIS VIRUS

CONGENITAL damage to the fetal central nervous system by various infectious agents has attracted a great deal of attention within the past few years. That maternal rubella, a virus disease, can bring about profound changes in the fetus has been established by critical clinical observations in human subjects. Likewise, toxoplasmosis, a protozoan infection, produces severe damage in the central nervous system of the human fetus, yet the mother of such offspring may show no overt signs of the infection.

With the recent growing interest in viruses which invade the central nervous system and with increase in knowledge concerning their behavior, the possibility of congenital transfer of such agents has been considered. As early as 1943 in a report entitled "Western Equine Encephalomyelitis in Infants," Medovy[1] cited two examples of encephalitis occurring in newborn infants on the third and fourth days of life. In each instance the blood of both the mother and her child showed significant titer of antibody against the virus of Western equine encephalomyelitis. In summarizing his findings, Medovy emphasizes "the necessity for considering the diagnosis of equine encephalomyelitis in infants showing spasticity and mental retardation."

In view of these clinical deductions based on human cases, it is of considerable interest that Japanese B, another arthropod-borne viral agent of encephalitis, has been shown capable of producing congenital damage of the central nervous system in swine. In the November, 1950, issue of the *Proceedings of the Society for Experimental Biology and Medicine*, Kenneth F. Burns[2] presents an excellent account of "congenital Japanese B encephalitis in swine." He reports that an epizootic in swine occurred in Japan during the years 1947 and 1948, concurrent with large epidemics of Japanese B encephalitis in Equidae and in human subjects, the year 1948 marking the largest epidemic on record in this area. Burns made the significant observation that a large number of stillbirths was reported among swine during August and September of 1947 and also of 1948, "with morbidity approximating 60 to 70 percent of the pregnant animals." Further investigations revealed that swine had been affected similarly during the great Japanese epidemic of encephalitis in 1935, and a serum survey of swine in the area yielded information which suggested a high incidence of inapparent infection with the virus of Japanese B encephalitis.

Pregnant females, apparently normal, gave birth to their young at or near the expected date of delivery. In some instances all the piglets in a litter were dead; in other instances, live, dead, and moribund piglets were observed in the same litter. It is highly significant that most of the young which appeared to be normal in development, were weak and unable to stand, and some which seemed normal at birth later developed signs of central nervous system involvement. Post-mortem findings on the piglets included encephalomalacia and internal hydrocephalus. Microscopic findings were consistent with the diagnosis of nonpurulent encephalitis. The maternal animals delivering the

abnormal piglets appeared to be in good health and, with the exception of anorexia and slight fever at varying periods during the pregnancy, had shown no recognizable signs of illness.

During the last week of July, 1948, Burns had an opportunity to study a litter of five newborn pigs in some detail. One newborn animal appeared normal in size and was followed through adolescence, showing no detectable abnormalities. One piglet was moribund at birth. The remaining three were too weak to stand or nurse and expired within from forty-eight to seventy-two hours after birth. These three were studied carefully. Gross and microscopic studies revealed changes typical of viral encephalitis. From the brain tissue of each of the three newborn pigs, an infectious agent was isolated which was identified by appropriate means as the virus of Japanese B encephalitis.

These studies present conclusive evidence that congenital damage of the central nervous system can be brought about in swine by the virus of an arthropod-borne encephalitis, and that the pregnant animal giving birth to such infected offspring may show little or no indication of illness during pregnancy, during delivery, or in the post-partum period.

Within recent years general interest in children who are born with central nervous system defects has been increasing. Despite great advances, however, a significant number of them still remains unexplained so far as etiology is concerned. It is possible that some of these children may have been damaged by congenital viral infection.

RUSSELL J. BLATTNER

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1. Medovy, Harry: Western Equine Encephalomyelitis in Infants, J. PEDIAT. 22: 308, 1943.
2. Burns, Kenneth F.: Congenital Japanese B Encephalitis Infection of Swine, Proc. Soc. Exper. Biol. & Med. 75: 621, 1950.

Correspondence

Dear Dr. Veeder:

This letter is to call attention to a minor error in the article entitled "Some Practical Aspects of Allergy," Journal of Pediatrics, November, 1950. On page 686 I find the statement that "pollen increases in the air during storms, *has normal peaks at noon and between midnight and dawn.*" (Italics mine.) In harmony with the last quoted phrase the author advises "staying indoors after sundown, keeping bedroom windows closed at night."

The idea that there is a normal high peak of pollen distribution between midnight and dawn is not in harmony with the known facts about the discharge of pollen from wind-pollinated plants and is totally at variance with the experience of those who have taken the trouble to make tests of the air at different periods of the day. Most wind-pollinated plants do not begin to shed pollen before daylight. I know of only one exception, namely, timothy, which opens a few of its anthers as early as 2:00 A.M. However, there is normally no appreciable wind distribution of this pollen before sunrise. Of course, a sudden storm at any time during the day or night may result in a higher temporary incidence of atmospheric pollen than at any other time during the 24-hour period. But sudden storms are exceptions, not the rule. Wind velocities average lowest during the latter part of the night.

Drs. Barnes and Rooks[1] over a 7-day period of exposure of slides at 6-hour intervals in Iowa City found that 53% of the pollen deposit on test slides was caught between 6.00 A.M. and noon, 23% between noon and 6.00 P.M., 14% from 6:00 P.M. to midnight and only 10% from midnight to 6:00 A.M. My own experience has been very similar.[2, 3]

O. C. DURHAM
Chief Botanist, Abbott Laboratories.

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1. Barnes, M. E., and Rooks, R.: Ragweed Pollinosis; Some Practical Considerations, J. Iowa M. Soc. July, 1950.
2. Durham, O. C.: Cooperative Studies in Ragweed Pollen Incidence, Atmospheric Data From Twenty-Two Cities, J. Allergy 1: 12, 1929.
3. Durham, O. C.: Meteorologic Aspects of the National Ragweed Pollen Problem, J. Allergy 3: 58, 1931.

Dear Dr. Veeder:

Certain omissions in my article entitled, "Some Practical Aspects of Allergy," The Journal of Pediatrics, November, 1950, have been called to my attention.

Since the article could not be as detailed in all respects as one might have wished because of the extent of the subject matter, these things and possibly many others need further clarification. Dr. Durham mentions the matter of night pollination. The intent here was not to imply that plants pollinate between midnight and dawn but that pollen concentration may vary with temperature and other meteorological changes. Dr. Durham also reminds me of the excellent survey "Hayfever Holiday" published by the Pollen Survey Committee, Research Council of the American Academy of Allergy, O. C. Durham, Chairman, Abbott Laboratories, North Chicago, Ill. This comprehensive survey gives ragweed counts for principal communities for the entire United States and was revised in 1950.

One error in the text has been called to my attention by Dr. A. W. Frankland, who notes that the London County Council is a political body and that the asthma breathing exercises, which we mention in the paper, are actually the work of the Asthma Research Council as correctly quoted in the bibliography.

SUSAN C. DEES

News and Notes

Dr. Jacques M. Lewis of New York died Jan. 29, 1951, at Miami, Fla., where he was vacationing. He was 50 years of age. Dr. Lewis was president of the medical board of Beth Israel Hospital and attending peditrician of Bellevue. For a number of years he had been connected with the pediatric department of New York University School of Medicine, and only last year was made full professor. He was a member of the American Pediatric Society and the American Academy of Pediatrics.

Drs. William Dameshek, Professor of Clinical Medicine, Tufts University School of Medicine, Boston, Mass., Clement A. Finch, Associate Professor of Medicine, University of Washington School of Medicine, Seattle, Wash., and Robert W. Heinle, Associate Professor of Medicine, Western Reserve University School of Medicine, Cleveland, Ohio, will participate in a continuation course on Diseases of the Blood in Infancy and Childhood to be presented at the Center for Continuation Study April 16 to 18, 1951. The course is given under the direction of Drs. Irvine McQuarrie and Charles D. May, Department of Pediatrics, University of Minnesota.

The Second International Poliomyelitis Conference has been scheduled for September 3 to 7, 1951, at the Medicinsk-Anatomisk Institut of the University of Copenhagen, in Copenhagen, Denmark. The meeting is sponsored by the National Foundation for Infantile Paralysis of the United States and the Danish National Association for Infantile Paralysis. Prof. Niels Bohr of Copenhagen is the presiding President. The program includes thirty-two papers and discussions. Among these are "Pathology and Pathophysiology of Poliomyelitis," "The Coxsackie Group of the Viruses," "Differential Diagnosis in Acute Poliomyelitis," and the "Treatment of Poliomyelitis." Papers will be delivered in English, French, German, or Spanish with simultaneous interpretations as employed by the United Nations.

The Danish Royal Ministry for Foreign Affairs is extending invitations to sixty nations to send official delegates to the Conference who will report on poliomyelitis in their respective countries. Physicians and scientists interested in poliomyelitis are invited to attend.

Transportation and currency arrangements are being facilitated by Thomas Cook & Son, Wagon-Lits-Cook, and the American Express Company. Conference officials announced that the Swedish American Lines are making available the MS STOCKHOLM, which is scheduled to leave New York on August 25, and to arrive at Copenhagen on September 2.

Requests for hotel accommodations and information concerning the Conference may be obtained from the Secretariate of the Second International Poliomyelitis Conference, Statens Seruminstitut, 80 Amager Blvd., Copenhagen s, Denmark.

The 25th annual Parents' Magazine Medal for Distinguished Service to Children was presented to Dr. Clifford G. Grulee for his work as a pioneer and leader in the field of pediatrics. The Award was presented at a luncheon in New York City on January 31. Dr. Howard A. Rusk was the guest speaker.

The Gesell Institute of Child Development, 310 Prospect St., New Haven, Conn., was founded in March, 1950, and has been incorporated as a private nonprofit organization for the purpose of continuing and expanding the clinical, research, and teaching services which its staff members had carried on for many years as the Clinic of Child Development at the Yale University School of Medicine. Incorporators were: Dr. Frances L. Ilg, Dr. Louise Bates Ames, and Miss Janet Learned who constitute the Board of Directors. Other corporation members are: Dr. Arnold Gesell and Robert Upjohn Redpath, Jr. A Scientific Advisory Board has been formed and includes the

following members: Prof. Wendell C. Bennett, Prof. Arthur T. Jersild, Dr. William H. Sheldon, Dr. Benjamin Spock, and Dr. Helen Thompson. The staff of the Institute at present consists of: Dr. Ilg, Acting Director, Dr. Ames, Research Associate, and Miss Learned, Preschool Specialist. Dr. Gesell is Consultant in Research.

The **American Board of Pediatrics** announces the following dates for oral examination:

New Orleans, La., March 2, 3, and 4, 1951
Cincinnati, Ohio, March 30, 31, and April 1, 1951
Atlantic City, N. J., May 5, 6, and 7, 1951

Book Reviews

Endocrine Disorders in Childhood and Adolescence. Lawson Wilkins, M.D., Springfield, Ill., 1950, Charles C Thomas, 408 pages, 411 illustrations. Price $13.00.

Endocrinology has been one of the most intriguing fields of medicine, as well as one of the most perplexing to the practitioner. It has, moreover, been a field in which there has been much hokum, and where flights of fantasy have tended at times to outweigh facts and straight thinking, and, unfortunately, it has been somewhat tainted with commercialism. Many years ago a distinguished American physiologist referred to it as the "graveyard" of many promising young medical men.

Over the years, however, a group of men, including several pediatricians, have approached the subject with the zeal and caution of true scientific investigation. One of this group is Lawson Wilkins, Associate Professor of Pediatrics at the Johns Hopkins Hospital. Based on his careful studies and investigations over many years, he has written a book on the diagnosis and treatment of the endocrine diseases in childhood and adolescence which is one of the most distinguished pediatric texts that has appeared in years. Some of the material, particularly the illustrations and charts, has been shown at the scientific exhibits associated with pediatric meetings in recent years where it has been of outstanding interest. In this text this has been augmented and brought together and made available to the clinician and practitioner.

In the first two of the twenty-one chapters in the book, the relation of extrinsic and genetic factors to growth and development is considered, and the various endocrine hormones and the part played by each. One of the more interesting and illuminating tables in the book, on the frequency of endocrine disorders, is found in this section. In a thirteen-year period prior to March, 1949, there were approximately 73,000 new patients seen at the Harriet Lane Home. Nine hundred ninety-seven, or approximately one in seventy-three, were referred to the endocrine clinic for study on the suspicion that there might be an endocrine disorder present. In these 997, a definite diagnosis of endocrine disorder was made in only 233, or about one-fourth of the referrals, and one in every 315 new patients seen over this period. An almost equal number, 236, were patients with obesity of dietary and constitutional origin without endocrine factors, and 207 patients had other abnormalities not involving the endocrine systems. Thus, in over half of the patients referred for study because of "suspicion," an endocrinopathy was eliminated. These figures should lead the practitioner to stop and reflect before looking on every disturbance in growth and development as due to some endocrine disorder.

The next two chapters take up the methods of endocrine study including tests of hormonal function.

The remaining seventeen chapters consider specific disorders. There are three chapters on thyroid disorders. In 146 of the 233 patients with endocrine disorders, the thyroid gland was involved. After a discussion of the specific thyroid conditions, including an excellent bibliography, each section is followed by an atlas presenting a graphic discussion of patients and illustrating the condition. It is a remarkable collection of unusually excellent photographs and charts.

In a similar way, the subjects of dwarfism, sexual precocity, sexual infantilism, adrenal disorders, pituitary disorders, heterosexual development, diabetes insipidus, and diseases of the calcium and carbohydrate mechanism are presented in subsequent chapters. The last two chapters discuss obesity and congenital anomalies that are sometimes mistaken for endocrinopathies.

The book is "atlas" size and is beautifully printed with unusually clear plates and charts. In the opinion of the reviewer, it is perhaps the most important pediatric text that has appeared in years. It is a text that American pediatricians can regard with pride as it reflects the sound scientific development of pediatrics in the United States in recent years. It is of great credit to the author and his associates at the Hopkins pediatric clinic. B.S.V.

Methods in Medicine. George R. Herrmann, M.D., St. Louis, 1950, The C. V. Mosby Co., 488 pages. Price $7.50.

This book is the second edition of *The Manual of the Medical Service of George Dock, M.D., Sc.D.,* and was written as a Festschrift in honor of Dr. Dock's ninetieth birthday. The manual "was planned as a practical ward or bedside guide for the clinical investigation of the common and some of the more rare conditions. Sound minimal requirements for the systematic diagnostic study, case recording, emergency case study and handling, scientific medical management, and dietetic therapy are outlined" in its chapters.

The first edition was written twenty-six years ago, and the second edition has been completely revised and brought up to date. While written by an internist for assistance in the practice of adult medicine, it contains much information equally valuable to the pediatrician. HARTMANN

Psychosomatic Medicine: Its Principles and Applications. Franz Alexander, M.D., New York, W. W. Norton & Co., 300 pages. Price $4.00.

Dr. Alexander writes with great clarity on a subject which has been his particular interest for many years. In this book he presents a working concept of the psychosomatic method and, although the problems are sometimes oversimplified, his approach is one which should be useful to many medical practitioners who are interested in understanding and meeting the emotional needs of patients. It should be of special interest to pediatricians for whom the field of psychosomatic medicine has not been as thoroughly explored as with adults.

S. R. WARSON

The Prognosis of Exudative Pleurisy in Children. Herbert Nathhorst, Stockholm. Supp. XVII Acta Tuberculosea Scandinavica.

This is a monograph giving the details of a study of 594 children under 16 years of age who had been treated at hospitals in Gothenburg and Stockholm for an exudative pleurisy. A group of 515 healthy tuberculin-positive children was used for controls in evaluating the statistics. In 65 per cent the onset of the pleurisy was acute, and in 35 per cent, insidious. The period of high incidence of development was March to May. 6.2 per cent of the parents of the children with pleurisy died of tuberculosis against an expectancy of 3.3 per cent. Only 0.7 per cent of the pleurisy series and 1.9 per cent of the control had rheumatic fever. In 78 per cent of the pleurisy cases a primary pulmonary focus was found in the roentgenogram.

From a prognostic standpoint, the chief purpose of the study, it was found that 53 of the 595 patients had died of tuberculosis (28 pulmonary type) against an expectancy of 10 if the risk were the same as for the general population. There is less risk of death for the child in the 0 to 9-year age group who develops pleurisy than for a child 10 to 16 years of age at the time of its development. Of the 595 children with pleurisy, 112 subsequently developed clinical tuberculosis (including the 53 deaths noted above) in contrast to only 16 of the 515 tuberculin-positive control group.

Public Health Is People. Ethel L. Ginsburg, New York, 1950, The Commonwealth Fund, 231 pages. Price $1.75.

This is a report of an institute on the subject of mental health in public health held at Berkeley in 1948, sponsored by the Commonwealth Fund and the State Department

of Health of California. The institute was held for a student body of thirty health officers and was conducted by three pediatricians, eight psychiatrists, and five public health officers. A large part of the institute was taken up with a discussion of the reactions of people to public health proposals, and the importance of a personal interest in dealing with people from a public health viewpoint is stressed. The procedures by which different types of experts in pediatrics, psychiatry, and public health adjusted themselves in working together is considered. The report is of particular interest to those who are handling people in groups, as public health officers, and is of lesser interest to practicing physicians.

Year Book of Pediatrics, 1950. Edited by Henry G. Poncher, M.D., and Julius B. Richmond, M.D., Chicago, The Year Book Publishers. Price $5.00.

This volume marks the 50th Anniversary of the Year Books. The occasion is observed by a number of "guest editorials" introducing some of the chapters and subjects, written by pediatricians whose work has been centered in the respective fields. It is a difficult task to summarize past accomplishments or the present status in a few hundred works, and some of the guests have quite "muffed the ball." On the other hand, some, as Helen Taussig on "50 Years in Congenital Malformations of the Heart," have done a remarkable job. The editors themselves have written an excellent editorial chapter of the trends or progress of pediatrics in the year covered, July, 1949, to July, 1950, in which the outstanding development of interest is the experimental use of ACTH and cortisone in various conditions.

The editors have made an excellent choice in the material selected for abstracting and reviewing from the world-wide literature on pediatrics which has become enormous. We were happy to find that the editors have continued to add pertinent remarks or discussion to many of the articles reviewed. The abstracting or reviewing itself is excellent and the reviewer who has followed the Year Book for many years feels the 50th Anniversary number has reached a "high." A text which survives fifty years as this has done must survive on merit. If the selection of material and editing continue on the same high level as the 1950 issue, someone fifty years from now will be reviewing the "Year Book of Pediatrics."

The Rhesus Danger. Its Medical, Moral and Legal Aspects. R. N. C. McCurdy, M.B., Ch.B., D.P.H., London, 1950, William Heinemann, 138 pages. Price 5 shillings.

This is an interesting and unusual discussion of the problems resulting from Rh incompatibility from which 664 children died in England in 1947. In the first section comprising about a third of the text, the author presents a clear, readable account of the medical background as regards blood groups, the discovery of the Rh factor and the Rh groups, the effects of sensitization, and the treatment of hemolytic disease. It is an excellent compilation, and the author makes no reference to any work of his own. It is "Part II: Some Wider Issues" that is most unusual. As the author states, the "Rh is the personal problem of a minority, but how it is resolved is a small but important social problem for the majority." The question at issue is what is a married couple to do when they unexpectedly find themselves with an Rh incompatibility which prevents them from having normal children. The solution raises the fundamental question of the purpose of marriage. The author presents a most interesting discussion of various possibilities toward a solution which involve the moral and legal aspects of contraception, sterilization, abortion, artificial insemination from a compatible male, adoption, and divorce. While the references are chiefly to English moral, social, and legal discussions and viewpoints, the question at issue is applicable to the United States. It is a most unique and interesting discussion of the problems resulting from the Rh, written by "one who must himself make up his mind on many of these questions because a child of the writer's was among the 664, and another will be numbered among those who died from the same cause in 1948." The book shows thorough study of a complex and difficult problem. It is a problem that must be settled on a personal and individual basis, and the book can well be recommended to educated parents who are faced with the condition as a personal problem.

Editor's Column

PEDIATRICS AND PSYCHIATRY

THE thoughtful and scholarly discussion of pediatrics and psychiatry in this issue by Langley Porter,* to whom the October issue of the JOURNAL was dedicated on the occasion of his eightieth birthday, recalled to mind the discussions of "pediatric psychiatry" by the late Joseph Brennemann which were published some twenty years ago. It led us to reread them after many years, and we found them as delightful and fresh and stimulating as when they were first published.

We well recall the furor which followed the first essay. It had the intriguing title of "The Menace of Psychiatry"† and took issue with some of the trends of psychiatry which had been developing in the decade of the twenties. It was, and is still, an extremely provoking discussion, and coming as it did from one of the most distinguished pediatric clinicians of his time, created much discussion among pediatricians and psychiatrists. It led to the second essay on "Pediatric Psychology and the Child Guidance Movement"‡ which was delivered by invitation before a psychiatric society. Brennemann clearly foresaw the role of the pediatrician, and the need for the development of men like Aldrich, Spock, and Senn in the field. We know of no more profitable way for the younger generation of pediatricians to spend an evening than to read these two essays by Brennemann, whose name to them usually means only the editor of a system of pediatrics.

We wonder if the future will see scholarly and thinking pediatric leaders of the type of Porter and Brennemann. Or will the pediatrician be so engulfed by the tremendous advances of scientific medicine that he will become merely a highly skilled artisan. Brennemann placed the basis of many of the child's problems of twenty years ago on the mechanical complexity of his environment, and the shortcomings of popular education. After rereading these two articles one can imagine what his comments would have been today with the development of television and the parental education features of the nursery school movement in the last two decades. One thing we can be sure of is that it would be rare and racy reading.

B.S.V.

"COURRIER"

THE JOURNAL extends greetings and felicitations to *Courrier*, the new monthly journal of the International Children's Centre in Paris, whose first issue reached this side of the ocean shortly after the New Year. The journal is bilingual, with the leading article by Dr. Robert Debré on the purpose of the center and its founding by UNICEF, first appearing in French, and second, in English. The same repetition occurs in the third section which is devoted to informa-

*Porter, Langley: The Pediatrician Looks at Psychiatry, p. 275.

†Brennemann, Joseph: The Menace of Psychiatry, Am. J. Dis. Child. 42: 376, 1931.

‡Brennemann, Joseph: Pediatric Psychology and the Child Guidance Movement, J. PEDIAT. 2: 1, 1933.

tion concerning work with children in various parts of the world.

Most of the issue is taken up by a department of "Analytical Bibliography." Abstracts are classified under some forty main headings beginning with Allergy and ending with Teaching. The abstracts are brief and descriptive rather than critical. In this issue nearly 500 titles of pediatric interest are included from over 150 medical journals from all parts of the world. About a third of these are American journals. An illustration will best give the idea of how the abstracting is done.

RAVITCH (M. M.), McCUNE (R. M.). Intussusception in infants and children. *(Invagination chez le nourrisson et l'enfant.)* J. Pediatr., U.S.A., vol. 37, no. 2, Aug. 1950, pp. 153-173 (2 tabl., 8 fig., 4 radios.).

36

Analyse clinque de 152 cas. Discussion du traitement: lavement baryté sous contrôle radioscopique, avec une thérapeutique préopératoire, au cours des premières 24 heures.

Clinical analysis of 152 cases. Discussion of treatment: Baryum enema under fluoroscopic control, with preoperative treatment, in the first 24 hours.

The *Courrier* will be published ten times a year and will follow the same general form with "one or two original articles of universal interest and scientific value on some special problem," the bibliography section, and the information section. The annual subscription has been placed at 2,000 French francs (around 350 for $1.00 at present exchange rates) for foreign countries. Dr. Raymond Mande is the Editor.

In connection with the analytical bibliographies, *Courrier* offers an important service to pediatric research workers. Microfilms of a given article will be furnished free of charge and may be ordered by the number given each abstract; for example, "36" in the illustration quoted above. Should a photostatic copy, or a photographic print of an article be wanted, it will be furnished at a cost of 80 French francs per page or double page. The *Courrier* office is located at the International Children's Centre, 2 bis, Avenue du Parc de Passy, Paris (16e), France.

NEW JOURNAL FORMAT

MUCH favorable comment has been received on the change in format which was made in the January issue of the JOURNAL. Most 7 x 10 inch monthly medical journals, as the JOURNAL in the past, use a single 5 inch column of 10 point type. This width necessitates a lateral shifting of the eyes to read a line which is tiring to the eyes. A few use a 4½ inch column, which reduces the extent of but does not eliminate the shifting. Most well-printed novels use a 3¾ to 4 inch line. While a 5 inch column is tiring to the eyes in 10 point type, in 8 point it is almost unreadable for long articles. Some years ago the JOURNAL discontinued the use of 8 point type except for News and Notes and Book Reviews on the simple grounds that if an article or report was worth publishing, it deserved to be printed in type that could be read without producing eyestrain. The use of 10 point type set "solid" was introduced at that time for case histories and other material usually set in small type. But the problem of lateral shifting of the eyes still remained with the 5 inch column.